Evaluation of a Shorter 12h Acetylcysteine Regimen & Development of a Simpler Acetylcysteine (SNAP) Protocol for the Treatment of Paracetamol Poisoning

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Abstract

Paracetamol is the commonest drug involved in hospital admissions with poisoning in the UK. Acetylcysteine (NAC) is the antidote of choice for treatment of paracetamol overdose, but the original 3-bag NAC regimen, designed in Edinburgh, is associated with infusion-related adverse reactions related to high peak plasma acetylcysteine concentrations from the high loading infusion of 600mg/kg/h. The Scottish and Newcastle Antiemetic Pre-treatment (SNAP) study has shown that a simpler 12 h regimen (SNAP) consisting of a reduced loading infusion rate of 50mg/kg/h, causes significantly fewer adverse reactions (1). The SNAP regimen was implemented in 3 UK hospitals with the approval of their local medicines management committees with prospective audit of clinical outcomes.

In this thesis, I have compared the efficacy in preventing hepatotoxicity of a 12h ('SNAP') regimen with the conventional 21 h NAC regimen used to treat paracetamol poisoning, including in patients at high risk of developing hepatotoxicity. Secondly, I have developed and validated a simple clinical decision rule for safe discharge of patients at the end of the 12h NAC treatment. Thirdly, I have developed a simpler 12 h NAC ('SNAP') protocol and care pathway to facilitate implementation in clinical practice.

The major findings and conclusions of the thesis are: i) development of hepatotoxicity (peak ALT >1000) and hepatic synthetic dysfunction (INR greater than 2) in patients treated with the SNAP regimen were not significantly different compared to the conventional regimen both in high-risk and low-risk patients (14.6% SNAP vs 15.2% standard, 95% CI, - 8.2 to 9.8), and (3.2% SNAP vs 2.6% standard, 95% CI, - 0.7 to 1.8), respectively; ii) paracetamol-aminotransferase multiplication product (APAP×AT) >1500 mg L^{-1}× IU L^{-1} h is a predictor of hepatotoxicity in patients treated with NAC and an important confounding variable, particularly in patients presenting late (P=0.001); iii) The SNAP regimen can interfere with coagulation activity with a median INR increase of 0.3 from baseline, even in the absence of liver injury, indicating that re-measurement of the INR at least 24 h post exposure if there is no other evidence of hepatic injury can avoid unnecessary additional treatment with NAC; iv) a simple clinical decision rule (paracetamol <10 and ALT≤ ULN, and ALT not doubled or more than doubled from admission value) accurately predicted patients who were eligible to discharge

safely after a shorter 12 h SNAP regimen with 100% positively predictive value, which can be used to facilitate earlier discharge of low-risk patients.

Author's declaration

I, Amani Alrossies, declare that this thesis represents my own work which has been submitted for the degree of Doctor of Philosophy at Newcastle University.

I certify that none of the material covered in this thesis has been previously submitted in whole or in part for consideration for any other academic degree or professional qualification. I confirm that work done by others is clearly acknowledged and any published work is clearly attributed and the source stated.

I have read the University's current research ethics guidelines and accept responsibility for the handling of patient's data in accordance with the Data Protection Act 1998 and guidelines in Newcastle Hospitals NHS Foundation Trust.

Amani Alrossies

February 2022

Dedication

I dedicate this work for my mum Munira, my dad Saleh, and my brother Abdul-aziz, who never saw the completion of this adventure.

I also dedicate my thesis to my kids Mashhour, Mohammed and Abdul-aziz, whom I can't force myself to stop loving.

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Conference presentations and abstracts

1. AlRossies A, Potts A, Hill SL, Wood DM, Dargan PI, Thanacoody HKR, Thomas SHL. **Evaluation of a shorter 12h acetylcysteine regimen and development of a simpler acetylcysteine (SNAP) protocol for the treatment of paracetamol poisoning.** North East Postgraduate Conference 2018, November 9, 2018 at Newcastle Civic Centre, UK. (Appendix A-1)

2. Amani S Alrossies, Ruben HK Thanacoody, James Harnett, Kerry Layne, John RH Archer, Simon L Hill, David M Wood, Paul I Dargan, Simon HL Thomas. **Efficacy of a shorter 12h intravenous acetylcysteine regimen following single acute paracetamol overdose.** British Pharmacology Society Meeting 2018, December 20, 2018 at the Queen Elizabeth II Conference Centre, London. (Appendix A-2)

3. Amani S Alrossies, Ruben HK Thanacoody, James Harnett, Kerry Layne, John RH Archer, Simon L Hill, David M Wood, Paul I Dargan, Simon HL Thomas. **Derivation of a clinical decision rule for early discharge of patients with paracetamol poisoning treated with a shorter 12-hour acetylcysteine regimen**. British Pharmacology Society Meeting 2018, December 20, 2018 at the Queen Elizabeth II Conference Centre, London. (Appendix A-3)

4. Amani S. Alrossies, David Wood, Paul I. Dargan, Simon H. L. Thomas, Ruben H. K. Thanacoody. **Derivation of a clinical decision rule allowing earlier discharge of patients with paracetamol poisoning after a shorter 12-hour acetylcysteine (SNAP) protocol.** 39th International Congress of the European Association of Poisons Centres and Clinical Toxicologists, May 24, 2019, Napoli, Italy. (Appendix A-4)

5. Alrossies AS, James Harnett, John RH Archer, Simon L Hill, David M Wood, Paul I Dargan, Simon HL Thomas, Ruben HK Thanacoody. **Efficacy of a 12h intravenous acetylcysteine (SNAP) regimen following single acute paracetamol overdose stratified by risk of paracetamol-induced hepatotoxicity.** British Pharmacology Society Meeting 2019, December 19, 2019 at Cromdale Hall, Edinburgh International Conference Centre, UK. (Appendix A-5)

6. AlRossies A, Potts A, Hill SL, Wood DM, Dargan PI, Thanacoody HKR, Thomas SHL. **Effect of a 12-hour intravenous acetylcysteine (SNAP) regimen on the International Normalized Ratio (INR).** 41st International

Congress of the European Association of Poisons Centres and Clinical Toxicologists, May 27, 2021. Virtual Congress platform. (Appendix A-6)

7. AlRossies A, Potts A, Hill SL, Wood DM, Dargan PI, Thanacoody HKR, Thomas SHL**. Efficacy of a 12h intravenous acetylcysteine (SNAP) regimen following single acute paracetamol overdose.** 41st International Congress of the European Association of Poisons Centres and Clinical Toxicologists, May 28, 2021. Virtual Congress platform. (Appendix A-7)

8. Alrossies AS, Wood DM, Dargan PI, Thomas SHL, Thanacoody HKR. **Efficacy of a 12h intravenous acetylcysteine (SNAP) regimen in patients at high risk of hepatotoxicity following single acute paracetamol overdose.** The British Toxicology Society Annual Congress 2022, April 5th 2022, Hilton Newcastle Gateshead, UK. (Appendix A-8)

Abbreviations

ALT	alanine transaminase.
APAP	N -acetyl-p -aminophenol (paracetamol).
APAP×AT	paracetamol-aminotransferase multiplication product.
GSH	Glutathione.
INR	International Normalized Ratio (a ratio of the patient's PT as compared to a laboratory normative PT value).
MHRA	Medicines and Healthcare Products Regulatory Agency.
NAARs	Non-allergic anaphylactic reactions.
NAC	N- Acetylcysteine.
NPIS	National Poisons Information Service.
NAPQI	N-acetyl-p-benzo-quinoneimine.
PT	prothrombin time.
SNAP	Scottish and Newcastle Antiemetic Pre-treatment.
ULN	Upper Limit of Normal.

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Chapter 1 Introduction

1.1. Paracetamol

Paracetamol is an analgesic and antipyretic agent that dominates the list of non-prescription medicines consumed in the world. Compared to aspirin, paracetamol is better tolerated and has a wide margin of safety between the therapeutic dose (1000 mg) and toxic dose (>4000 mg)(2). However, ingestion exceeding the recommended daily dose can cause fulminant hepatic failure (3) and death, and paracetamol can be more toxic in overdose than aspirin (4, 5).

1.1.2. History of paracetamol development

Before the discovery of paracetamol, in the first half of the 19th century, quinine derivatives and Cinchona bark powder were used for mild to moderate pain and high temperature. Due to quinine side effects and the cost of Cinchona, willow bark powder, which is much cheaper than Cinchona, was introduced in clinical used to reduce high temperature in 1827(6). In 1899, acetylsalicylic acid was developed as a pharmaceutical product from willow bark to be used as an antipyretic by the Bayer Company under the name of Aspirin®(7).

In the second half of the 19th century, the aromatic compound aniline, isolated from coal-tar, was first synthesised in 1863 in Germany by the Friedrich Bayer Company(8). In 1886, two young scientists, Arnold Cahn and Paul Hepp, examined the effect of naphthalene (an aniline derivative) as an antiseptic for intestinal parasite infestation, and they noticed that although ineffective for treating the parasite, fever was reduced. After more than one dose, the two physicians detected that a pharmacist mistakenly dispensed acetanilide instead of naphthalene. Acetanilide is another aniline derivative used as an intermediate in the synthesis of sulpha group and also a building block in penicillin preparation. One year after this mistake, acetanilide was marketed as an antipyretic with the trade name Antifebrin®. Ten years later, the Bayer Company synthesised p-nitrophenol (phenacetin®), also an aniline derivative, as a less toxic alternative to acetanilide. Phenacetin quickly gained popularity in most countries as an alternative to aspirin. However, the severe side effects after long-term use of aniline derivatives, phenacetin and acetanilide including methaemoglobinaemia,

which causes inability of red blood cells to effectively release oxygen to body tissues (cyanosis), led to their withdrawal from the market.

Paracetamol itself was discovered in the late 19th century, but it took half a century to develop it as a new pharmaceutical product. In 1893, Joseph von Mering, a German physiologist, in collaboration with chemists at the Bayer Company, first synthesised N-(4-hydroxyphenyl) ethanamide, a phenacetin metabolite, later called paracetamol (Europe) or acetaminophen (USA). Although their observation was that paracetamol is effective as an analgesic and antipyretic, they also found that it, like other aniline derivatives, caused cyanosis (9). Today, it is believed that von Mering might have used impure paracetamol in his investigation. Due to this, paracetamol was not used for over 40 years. During that time, methods to measure the amount of drug in the blood were developed in medical laboratories. In 1948, two biochemists (Flinn and Brodie) at Yale University demonstrated that N-acetyl-p-aminophenol (APAP) was the major metabolite of acetanilide in plasma and believed that this metabolite was responsible for analgesic activity. They found that ingestion of oral paracetamol had comparable effects to acetanilide on pain threshold in 12 subjects, with the distinct advantage of not causing methaemoglobin formation. A few years after this investigation, paracetamol was marketed under the name of acetaminophen in the United States in 1951 and paracetamol in Great Britain in 1956 (10, 11).

1.1.3. Mechanism of action of paracetamol

Although paracetamol has a long history, the mechanism of action remains unclear(12) but the most up-to-date evidence is that it acts within the central nervous system, involving combination of effects on prostaglandin production, on serotonergic, and on cannabinoid pathways(13).

The primary mechanism of action of paracetamol is through inhibition of brain prostaglandin E2 synthesis. The possible mechanism is that arachidonic acid required bifunctional enzymes to convert to prostaglandin H2 (PGH2). Those enzymes are cyclooxygenase to produce prostaglandin G2 (PGG2), unstable intermediate hydroperoxide, and peroxidase which converts the unstable intermediate to PGH2. It is believed that paracetamol acts as a reducing co-substrate at the site of peroxidase (**Figure 1-1**).

Paracetamol acts strongly as a reducing agent by blocking the peroxidase in the area where the peroxide level is very low such as in the intact cell. However, paracetamol is ineffective in tissues with high peroxide levels, such as platelets or inflammatory conditions. This might explain why paracetamol has low anti-inflammatory activity, as peroxide levels are high in peripheral sites of inflammation.

Paracetamol can produce antipyretic and analgesic effects at sites with low peroxide level such as vascular endothelial cells and neurons(13).

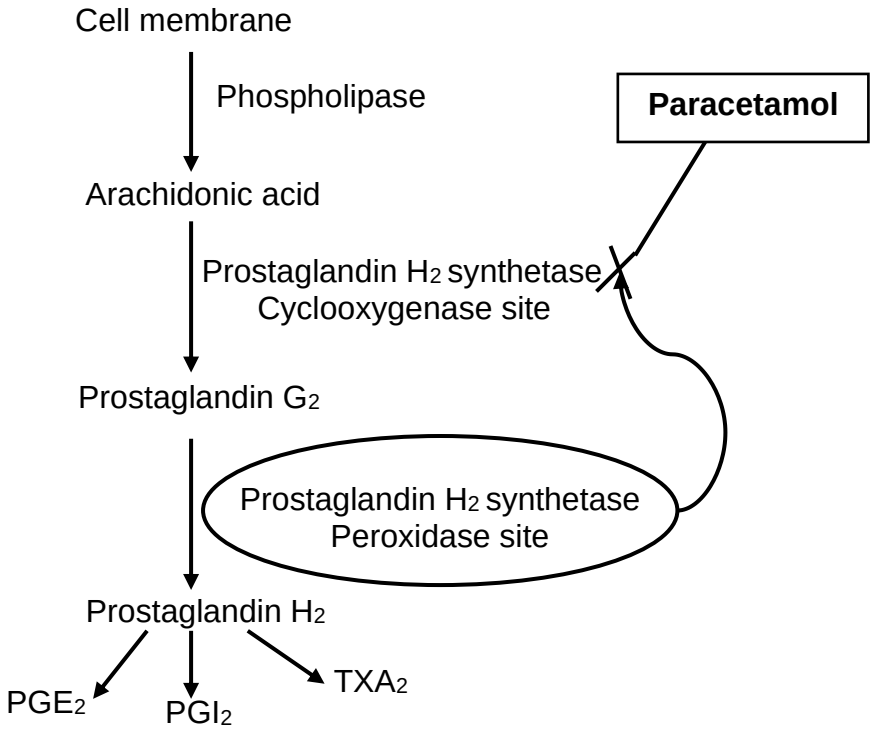


Figure 1-1: paracetamol mechanism of action on prostaglandin production(13)

Enhancement of endocannabinoid (CB1) receptor is another possible site of paracetamol action. Antinociceptive and antipyretic properties appear to result from increase in the level of endogenous cannabinoids (CBs). It is also thought that experience of relaxation, tranquillity, and euphoria reported by many paracetamol users are related to endogenous CBS(14). The exact mechanism of paracetamol on endocannabinoids is not fully identified, although the studies showed that fatty acid amide N-arachidonoylphenolamine (AM404) is the most important metabolite of paracetamol to induce analgesia and lower body

temperature through central nervous system effects. Once paracetamol is metabolised to p-aminophenol in the liver (**Figure** 1-2), this easily crosses the blood-brain barrier and is conjugated with arachidonic acid by fatty acid amide hydrolase to form AM404 in the brain. AM404 activates CB1 receptors indirectly through binding to vanilloid subtype 1 receptor (TRPV1) and it also acts as an inhibitor of cellular anandamide uptake resulting in increased levels of endogenous CBs (13).

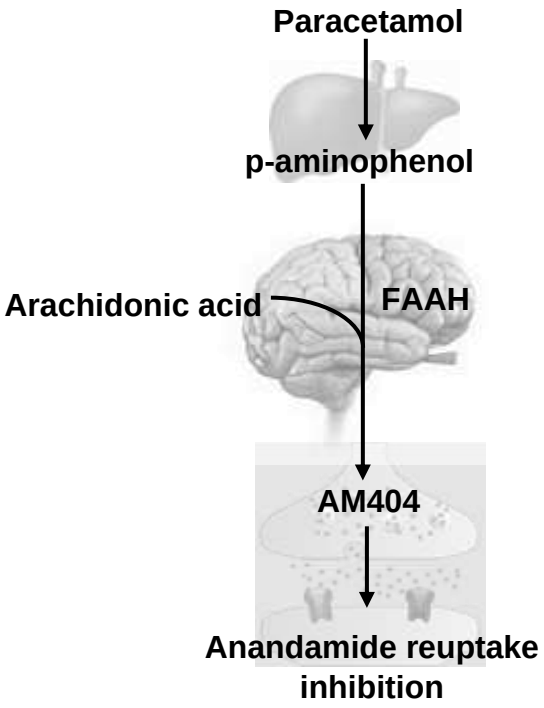


Figure 1-2**: Metabolic transformation of paracetamol to AM404, an endocannabinoid reuptake inhibitor(13)**

More recently, it has been suggested that paracetamol acts on serotonergic descending pain pathways as a 5-hydroxytryptamine (5-HT3) receptor agonist. This descending pathway has been shown to mediate the antinociceptive action(12). Most evidence suggests that paracetamol acts mainly centrally to produce its analgesic and antipyretic effects, and the primary mechanism of action is inhibition of prostaglandin production. Recently paracetamol has been shown to increase endogenous neurotransmitter systems including endogenous cannabinoids and serotonin (5-HT3) which enhance the anti-nociceptive effect of paracetamol.

1.1.4. Pharmacological effect

Paracetamol is classified as a non-opioid analgesic and is FDA-approved for fever and pain (mild to moderate). It is clinically effective for headaches, arthritis, painful inflammatory disorders, musculoskeletal pain, acute migraine headaches, postoperative pain, and perineal pain in the early postpartum period(15). Paracetamol acts mainly centrally as an anti-nociceptive and antipyretic(16) and has little anti-inflammatory and anti-platelet effects (17). It is also reported to have psychotropic effects including feeling of wellbeing, relaxation, or euphoria after paracetamol ingestion. The effect of paracetamol is dose dependent; antipyretic activity occurs at a lower dose than analgesic activity. When exceeding the recommended daily dose, toxicity increases rather than efficacy(18).

Anti-inflammatory activity:

Although paracetamol has poor anti-inflammatory effects peripherally, it could reduce inflammation through the inhibition prostaglandin H2-synthase (PGHS) in the brain. A number of studies showed a weak anti-inflammatory effect with high doses of paracetamol in animal models. It has also been recorded that paracetamol can suppress tissue swelling after dental surgery; nevertheless, it not very effective. In clinical care, paracetamol is usually effective for the pain associated with mild to moderate inflammation, such as sprains and contusions, but not in patients experiencing significant inflammation associated with rheumatoid arthritis or acute gout. It might be effective for rheumatoid arthritis only at very high doses, but this is limited by paracetamol toxicity (17).

Antipyretic activity:

Paracetamol acts centrally(19) to produce its antipyretic effect through the inhibition of synthesis and release of prostaglandin E2 (PGE2) in the cerebrospinal fluid and in the hypothalamic thermoregulatory centres(15). Paracetamol's anti-pyretic effect is dose-dependent; reduction in temperature is correlated with decreases in PGE2 concentrations in the brain and paracetamol concentrations in the blood. However, the normal anti-pyretic dose (650–1300 mg) had no effect in afebrile patients. After an oral dose, effects begin within 30 minutes and lasts at least 6 hours (20) (17).

Anti-analgesic activity:

Paracetamol produces a central analgesic effect through the activation of the descending serotonergic system, inhibition of prostaglandin (PG) synthesis and/or through an active metabolite influencing cannabinoid receptors (21). Paracetamol is indicated for mild-to-moderate and non-inflammatory pain; although it has been shown to reduce over 50% of acute non-specific type pain (22) such as acute postoperative pain, orthopaedic pain and tension headaches . Paracetamol has a rapid onset of analgesia, within 5–10 minutes after IV administration with a duration of 4 to 6 hours (20).

1.1.5. Pharmacokinetics/Metabolism

Paracetamol has high bioavailability and 80% of the oral dose is absorbed via the small intestine, with minimal absorption through the gastric mucosa. Therefore, food, drugs or disease that delay gastric emptying will affect the time to peak concentration in blood. In normal adults, the time to peak is 0.5 to 1.8 hours, and the onset of analgesia is within 15 to 30 minutes (23). When caffeine is administered concomitantly with paracetamol, it expedites the absorption of paracetamol, which might accelerate the analgesic effect. Paracetamol has a large volume of distribution with insignificant plasma protein binding, however, the binding to plasma protein might reach 43% after a toxic dose (22). In the liver, around 90% of the oral dose is metabolised by conjugation to non-toxic metabolites, which are excreted renally, whereas around 10% of the dose is oxidised by cytochrome P450 through the primary enzyme CYP2E1 to the highly toxic reactive metabolite, N-acetyl-p-benzo-quinoneimine (NAPQI), which is usually detoxified by conjugation with liver glutathione (24). However, NAPQI may accumulate in the liver as a result of overdose, or pre-existing hepatic injury, and cause liver damage. Although the elderly, neonates, malnutrition, and chronic alcohol abusers may have low glutathione stores and susceptibility to develop hepatotoxicity, dose adjustments are not recommended in those conditions. Dose adjustments might be recommended in patients with severe renal impairment (creatinine clearance 10–30 ml/min) as paracetamol elimination is 3 times slower than normal(13).

1.2. Paracetamol toxicity

1.2.1. Toxic dose

Ingestions above the recommended maximum therapeutic daily dose, which is 4g, or greater than 75 mg/kg as a single dose are considered a toxic dose and may lead to hepatotoxicity(25). Advice from the UK National Poisons Information Service (NPIS)(26) describes three types of paracetamol exposure. In the context of self-harm, ingestion of a toxic dose (75 mg/kg or more) over a period of one hour or less is considered as an acute overdose, while ingestion of a toxic dose over longer than one hour and in any 24-hour period is defined as a staggered overdose. Chronic therapeutic excess, on the other hand, is ingestion exceeding the licensed daily dose of 4g, usually with intent to treat pain or fever and without self-harm. The toxic dose could be consumed from one brand of paracetamol or from use of more than one paracetamol-containing product at the same time. Toxicity is unlikely to develop when the total amount of paracetamol ingested is less than 75 mg/kg. Ingestion of between 75 and 150 mg/kg within any 24-hour period is rarely toxic. Ingestions of greater than 150 mg/kg in any 24-hour period may cause severe toxicity. Although therapeutic doses of paracetamol are safe(27), there is limited evidence that use of 4 g/day over several days to weeks can cause some liver injury (28-30). A review of the evidence found elevation of ALT can occur patients who consumed 4 g paracetamol daily for at least 4 days(30), even though it usually resolves. This is thought to be idiosyncratic drug-induced liver injury (27, 30) resulting from risk factors, including genetic polymorphisms in CYP2E1, which is the most important enzyme involved in the detoxification of paracetamol to NAPQI. There is high inter-individual variations of CYP2E1 activity from complete deficiency of activity to ultra-rapid metabolisers which as a result, can increase or decrease the risk of hepatotoxicity in paracetamol poisoning(30).

1.2.2. Paracetamol metabolism and toxicity

The mechanism of paracetamol-induced hepatotoxicity has not been fully elucidated despite extensive investigations since the first case was recorded in mid-1966(31). Initially, in the mouse model, the primary mechanism of hepatotoxicity appeared to be due to hepatic glutathione depletion and protein adduct formation. Subsequent studies have showed that mitochondrial oxidant

Stress is considered to be a significant cause of hepatocyte death after paracetamol overdose in human (Figure 1-3)(32).

The mechanisms of paracetamol hepatotoxicity have been assumed to occur in four phases:

Phase 1: an induction phase, which involves significant glutathione (GSH) depletion and build-up of mitochondrial NAPQI-protein adducts.

Phase 2: mitochondrial oxidative/nitrosative stress, which is a critical requirement for induction of downstream signalling events through enhanced reactive oxygen species (ROS) formation and initiate activation of c-Jun N-terminal kinases (JNK).

Phase 3: Amplification phase, which produces hepatocyte necrosis through amplification of oxidative/nitrosative stress in mitochondria.

Phase 4: Degradation phase, where subsequent mitochondrial oxidant stress triggers the mitochondrial membrane permeability transition (MPT) pore, resulting in the collapse of the mitochondrial membrane potential, release of mitochondrial proteins, and finally cell necrosis(33, 34).

Induction (Metabolic) phase

The major part (approximately 90%) of therapeutic dose undergoes hepatic phase II metabolism to form 55 % glucuronide (APAP-glu) and 30% sulphate (APAP-sul), which are renally excreted(31). The critical toxic metabolic pathway is phase I metabolism of a small proportion of dose through CYP450 enzyme to the toxic oxidizing intermediate, NAPQI. Within therapeutic dose, the majority of NAPQI directly undergoes conjugation via sulfhydryl group in reduced GSH form to non-toxic mercapturic acid or cysteine conjugates. In excess paracetamol exposure, sulfation gets saturated initially, then glucuronidation which has higher level of capacity but is saturable after overdose. The limited conjugation capacity for paracetamol detoxification contributes to divert paracetamol metabolism to other pathways (Phase I) causing greater toxic metabolite formation and depleting glutathione stores in the hepatocyte, hence; the proportion of remaining unbound NAPQI accumulates. This free form of NAPQI binds covalently with sulfhydryl groups of mitochondrial proteins which are critical targets for NAPQI adduct formation(28).

Mitochondrial oxidative/nitrosative stress

Both glutathione depletion and mitochondrial protein adduct formation, from previous phase, enhance mitochondrial superoxide production such as Reactive Oxygen Species (ROS), which is the crucial event in the mechanism of toxicity. ROS play a role in the impairment of mitochondrial respiration and causing mitochondrial dysfunction. Oxidation stress involves generation of superoxide anion ($O2^{-}$) in mitochondria whilst nitrosative stress is activation through peroxynitrite formation (highly reactive radical $ONOO^{-}$), which results from a reaction between superoxide anion and nitric oxide (NO). Both superoxide anion (oxidation stress) and peroxynitrite anion (nitrosative stress) formation in mitochondria are important steps in the initiation of hepatotoxicity after paracetamol overdose but does not directly damage mitochondria (34).

Further oxidant stress is generated outside of the inner mitochondrial membrane. The initial superoxide formation activates redox sensitive mitogen-activated protein kinases (MAPKs) such as apoptosis signal regulating kinase1(ASK1), which activates and phosphorylates of c-Jun N-terminal protein kinases (JNK) (

Figure 1-3) (34).

Amplification of the mitochondrial oxidant stress

It is thought that JNK might amplify the initial oxidant stress, so JNK could play an essential role in the regulation of mitochondrial oxidant/nitrosative stress. After phosphorylation of c-JNK, the p-JNK form binds to Sab, a scaffold protein, located in the mitochondrial outer membrane (MOM). This inhibits the electron transport chain (ETC) and promotes release of superoxide. Superoxide ions in the mitochondria either react with NO to form peroxynitrite (an actual oxidant responsible for liver injury) or dismutase manganese superoxide (MnSOD) to form hydrogen peroxide and molecular oxygen. However, in paracetamol overdose, MnSOD is inactivated by peroxynitrite and hepatic GSH, endogenous scavengers of peroxynitrite, is depleted. This process results in amplification of oxidative/nitrosative stress with continuing further JNK activation and cell death(35, 36).

Degradation Phase

The principal mechanism in triggering downstream events of apoptotic cell death pathways is induction of the mitochondrial permeability transition (MPT). This event is initiated by translocation of activated JNK from the cytosol to the mitochondria, which also phosphorylates the pro-apoptotic protein Bax from the cytosol to the mitochondrial outer membrane. In addition, as iron-rich lysosome is sensitive to oxidative stress, it has been found that lysosome derived iron is taken up into mitochondria through the mitochondrial electro-genic calcium. Translocations of JNK, Bax, and iron into mitochondria contribute to open MPT, which leads to catastrophic collapse of mitochondrial membrane potential and impaired ATP synthesis. The activation of the MPT causes extensive release of mitochondrial proteins into cytosol such as cytochrome c, apoptosis-inducing factor (AIF), and endonuclease G, which cause nuclear DNA fragmentation and necrotic cell death.(33)

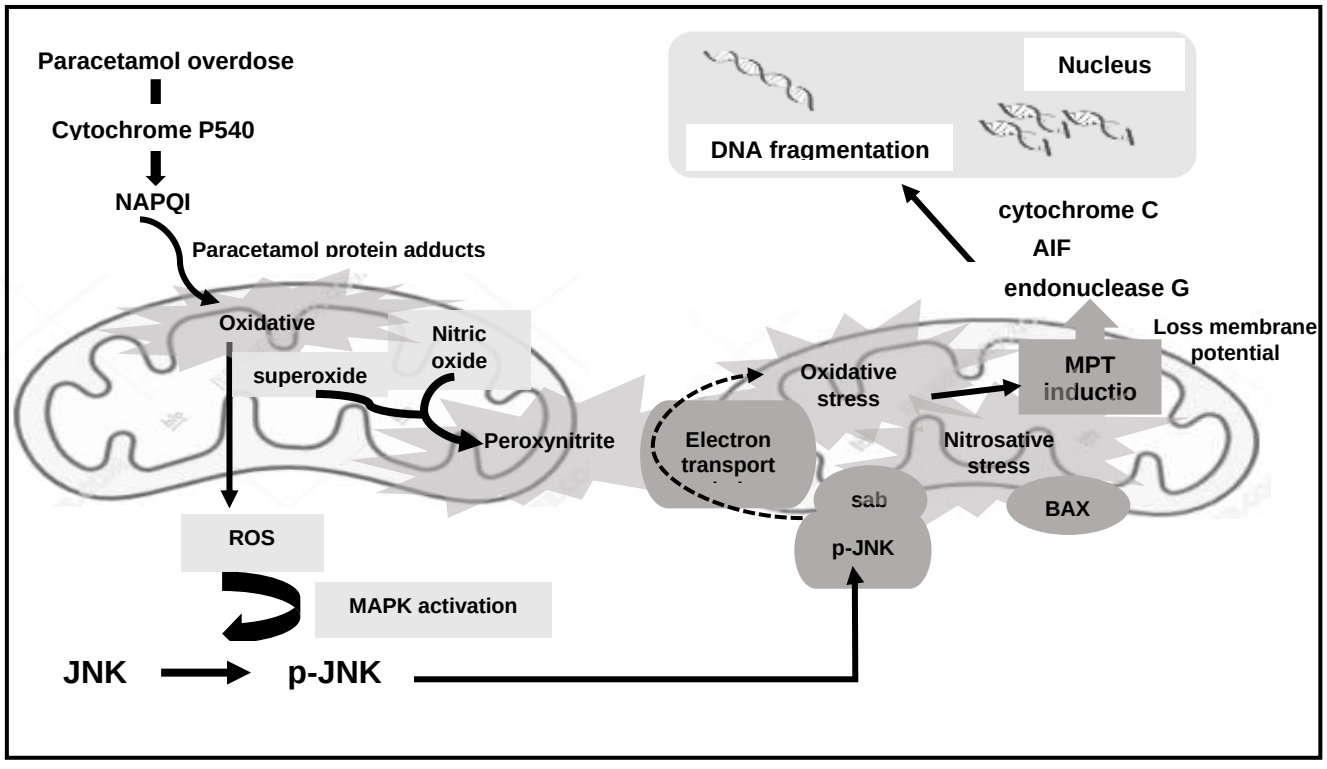


Figure 1-3: Paracetamol induced cell necrosis. [Redraw from reference (28)

1.2.3. Paracetamol toxicity

The well-known complication of paracetamol overdose is hepatic necrosis, although severe paracetamol poisoning can cause toxicity in other organ systems such as cardiovascular and renal failure. Pulmonary damage, and gastrointestinal complications such as pancreatitis have been rarely reported in presence of hepatic failure with paracetamol poisoning.(13)

Hepatotoxicity

Paracetamol overdose is responsible for up to 50% of all acute liver failure cases in the USA, Europe, and Great Britain (37-39). In the majority of cases of paracetamol toxicity, only mild signs of liver disease such as hepatitis, cholestasis or asymptomatic liver enzyme elevation are seen. Most cases of paracetamol-induced hepatotoxicity is due to intentional (suicide attempts) overdoses, which accounted for 52% compared to 48% for unintentional overdoses (40). Fatal hepatic injury can occur with a single overdose greater than 15g with attempted self-poisoning (37). During the first 24 hours of overdose, the common clinical manifestations are non-specific such as nausea, vomiting, anorexia, diarrhoea, and abdominal pain, while severe abdominal pain, hepatic tenderness, jaundice, and haemorrhage can occur as a result of liver failure, which usually appears after at least 48 hours. Lactic acidosis, hypoglycaemia, and coma might be present in the early stage of paracetamol poisoning, before the onset of hepatotoxicity in very severe poisoning, or in the later stages as a result of reduced hepatic clearance(41). Once hepatic encephalopathy develops, the risks of complications and death increase significantly(39). Although, hepatic failure can be effectively prevented by intravenous NAC given within 24 hours of overdose, liver transplant may be required once hepatic encephalopathy develops. Paracetamol overdose constitutes 20% of all liver transplant cases(40) with a 30% mortality rate (42). Overall, the mortality of patients admitted with paracetamol overdose treated with NAC therapy early is approximately 0.5%(43).

Cardiotoxicity

A few studies have reported that paracetamol poisoning could induce cardiotoxicity; although evidence for direct cardiotoxicity is weak (44). Direct cardiac toxicity may be caused by the toxic metabolite NAPQI, which acts as a direct toxin on the myocardium. Another possibility is indirect toxicity due to secondary depletion of sulfhydryl groups or excessive oxidative stress production, which results from hepatic toxicity. Sulfhydryl depletion may lead to paracetamol interfering with nitric oxide production, which might lead to coronary ischemia, whereas oxidative stress may cause cardiac arrhythmias. Although changes in the ECG and elevated serum creatine kinase might be seen in paracetamol poisoning cases, they are not specific indicators of paracetamol cardiotoxicity (45). There is no sensitive indicator to be used for cardiotoxicity assessment after paracetamol overdose currently.

Nephrotoxicity

Paracetamol-induced nephrotoxicity may also occur, sometimes in the absence of hepatic failure. The probability of development of acute renal injury secondary to paracetamol overdose is 1% to 2%(44) and 70% of cases are associated with hepatic damage(40). The most likely mechanism of renal toxicity in the kidney is formation of the toxic metabolite NAPQI by cytochrome P450, which is found in both liver and kidney; NAPQI forms adducts by binding with sulfhydryl group on cellular proteins, followed by cell death and tissue necrosis. This process has been demonstrated in both liver and kidney; however, the cytochrome P450 expression differs in each organ, which might explain the difference in incidence of renal and hepatic toxicity (46). The most common pathological renal abnormalities are acute tubular necrosis, interstitial nephritis, and distal tubular damage. Oliguric renal failure develops within 24-48 h usually in the context of hepatotoxicity or delayed after 48 hours in the context of hepatic failure. Direct renal insufficiency without hepatic impairment occurs only rarely, and mostly in patients with risk factors such as dehydration, nephrotoxic drug therapy, or pre-existing renal disorders(47).

1.2.4. Reports of toxicity

The most commonly reported pattern of paracetamol overdose is intentional overdose in the UK, while in the US it is accidental (48, 49). The proportion of

overdoses in the UK including paracetamol increased significantly from 14.3% in 1976 to 47.8% in 1993(11) , so the UK passed legislation in 1998 to reduce the incidence of paracetamol overdose by restricting the amount of paracetamol tablets that could be bought on a single occasion from pharmacy and retail outlets. This approach appeared effective in the UK leading to a 57% decline in the reported number of paracetamol overdose after introduction of pack-size legislation(50); in contrast, the USA has never enforced paracetamol sale restrictions and the proportion of acute liver failure cases resulting from paracetamol overdose has remained stable at 50% since 1998(51). Over 22 years (1992 -2014), paracetamol overdose has remained the most frequent cause of acute liver failure in both the UK and USA(51). In the UK, the median rate of hospital admissions for paracetamol poisoning per 100, 000 population increased significantly from 81.3 in 2007 to 100.7 in 2014, but the mortality rate from paracetamol poisoning has declined from 0.68% in 2005 to 0.35% in 2014(48), before increasing again in 2019. Australia has also not implemented a legal limit to the number of paracetamol tablets that can be purchased from retail outlets, and the most recent data showed a 44.3% increase in number of hospital admissions with paracetamol poisoning from 2008 to 2017, an increase in number of tablets taken per overdose from 15 in 2004 to 20 in 2017, but the number of paracetamol-related deaths has remained unchanged over 10 years (52). Overall, the reported numbers of hospital admissions and cases of liver injury attributed to paracetamol overdose have not changed despite reducing pack size of paracetamol(53).

1.2.5. Clinical risk factors for toxicity

Some patients with paracetamol overdose appear more susceptible to hepatotoxicity. Risk factors reported include:

Genetic variation

Paracetamol metabolism might be boosted or reduced because of genetic polymorphisms in CYP enzymes, for example, reduced activity of UGT (glucuronidation), SULT (sulphotransferase), GST (glutathione S-transferase), or enhanced activity of the CYP450 enzyme CYP2E1, which is involved in the bioactivation of paracetamol to NAPQI and by this mechanism could increase the risk of paracetamol related hepatotoxicity. However, it is unclear that genetic polymorphisms in paracetamol metabolism modulate risk. Comparative studies of

ethnic differences in paracetamol metabolism showed that the fractional recovery of mercapturic acid and cysteine conjugates of paracetamol was significantly (2x) higher in Caucasian than African populations(54), indicating more resistance of hepatotoxicity following paracetamol overdose in Africans(54, 55). However, the evidence is not strong enough to suggest one ethnicity is at higher risk over another (30, 40, 56).

Age

It was hypothesised that the elderly may be at higher risk for acute liver failure, liver transplantation and death as a result of paracetamol overdose as a result of changes in pharmacokinetics in older people, which might translate to increased risk of toxicity. Also, it is believed that younger people have larger hepatic cell mass, as well as better hepatic regeneration capacity. However, there is no conclusive evidence of changes of PK in the elderly to be able to determine whether older people at risk of hepatotoxicity or not(30, 40).

Nutritional status

Malnutrition is considered a risk factor as GSH reduction would limit the ability to detoxify NAPQI leading to increased risk of acute liver failure. However, some studies showed that even though people with poor nutritional state, such as anorexia nervosa, have low GSH stores, the rate of CYP2E1 activity is also diminished, offsetting the increased risk of paracetamol toxicity in these underweight patients. In fact, the evidence indicating malnutrition as a risk for paracetamol toxicity is mostly anecdotal from case reports and not sufficiently robust to justify malnutrition as a risk factor for paracetamol hepatotoxicity (30, 40).

Alcohol

Although case reports and retrospective studies suggest glutathione depletion and CYP2E1 induction in chronic alcoholics can exaggerate the risk of hepatoxicity in patients with paracetamol overdose(40), they were low quality clinical evidence(30). It is documented that daily ethanol consumption of 18 units or more might increase the probability of acute liver failure after paracetamol overdose. Prospective studies determined that a single therapeutic dose of paracetamol does not seem to be associated with increased susceptibility of acute liver failure in

chronic alcoholic users, especially if paracetamol is taken less than 8 hours from alcohol consumption. It has been suggested that the higher paracetamol-induced hepatotoxicity among these individuals might be due to the tendency of chronic alcoholics to delay seeking medical attention after paracetamol overdose, which would prolong time to initiate treatment, which may worsen outcomes. Nevertheless, it is still controversial whether chronic alcohol excess should be considered a risk factor for hepatotoxicity related to paracetamol overdose(30).

Potential drug interactions with paracetamol

It has been reported that certain pharmacological agents might interact with liver metabolism, resulting in either harmful or protective interactions. With regards to toxicity, the assumed mechanism and potential site of interaction of other drugs might be increased paracetamol oxidation, reduced conjugation, or depleted liver glutathione stores (reduced NAPQI detoxification), which result in increased NAPQI production. For example, anti-epileptic drugs, such as phenobarbital, phenytoin and carbamazepine, as well as anti-tuberculosis drugs, such as rifampicin, may increase paracetamol toxicity through induction of the oxidative pathway. Aside from oxidative stress, the interaction might be through saturation of the glucuronidation pathway, which might lead to shift of metabolism toward the oxidative phase. On the other hand, competitive inhibition of CYP450 enzymes might be potentially protective against paracetamol hepatotoxicity by reducing production of paracetamol toxic metabolites (NAPQI) but the evidence for this is insufficient(30, 40).

Chronic liver disease

There is concern that consumption of paracetamol in patients with chronic liver disease (CLD) may carry a higher risk of hepatic toxicity, but clinical studies of therapeutic doses of paracetamol in chronic liver disease do not show increased oxidative metabolism to toxic metabolites, or exhaustion of GSH store in CLD. Furthermore, a clinical study found that the increased half-life of paracetamol in cirrhotic patients did not cause substantial change in paracetamol accumulation or its excretion compared to controls. Besides, there is no good evidence to recommend dose reduction for patients with chronic liver disease (40).

1.3. Antidote treatment for paracetamol overdose

1.3.1. Glutathione Precursor Therapy

Activated charcoal, haemodialysis or haemoperfusion have a role in reducing absorption or enhancing elimination of paracetamol.(57). Before the role of glutathione in protecting the liver against toxic metabolites through binding to hepatic cells was demonstrated in 1973(58), there was no specific management to prevent hepatic injury after paracetamol overdose. Mitchell and his colleagues showed that glutathione precursors and sulfhydryl compounds such L-cysteine significantly reduced the covalent binding of NAPQI to hepatic cells. However L-cysteine is normally present at low concentrations in the hepatocyte due to rapid breakdown in the gastrointestinal tract (59). Other glutathione precursors such as methionine and cysteamine, which penetrate into the hepatocyte, were used to prevent hepatic necrosis after paracetamol overdose (60), but were only effective within the first few hours after ingestion of a toxic dose of paracetamol, and could cause gastrointestinal and central side effects following intravenous administration (60). Subsequently, NAC was suggested as an antidote as it is rapidly hydrolysed to the amino acid cysteine and it has been pharmaceutically available as a mucolytic for more than 50 years with a good safety profile (61).

1.3.2. N-Acetylcysteine (NAC)

It is now established that NAC mitigates the risk of liver injury after paracetamol poisoning by maintaining intracellular glutathione concentrations (58). In a study using radiolabelled NAC in mice, the liver, kidney and bone marrow were shown to be the three main organs for glutathione biosynthesis(62). Although there was hepatic uptake of radioactive NAC after injection in mice with maximum concentration at 45 minutes of injection, there was no significant increase in hepatic glutathione concentrations within 5 hours. There was a doubling of glutathione in the bladder and a 70% decrease in glutathione level in bone marrow. Another study indicates that there are two NAC isomers: the D-isomer is a non-physiological stereoisomer which is taken up by the liver 7 times more than the L-isomer. The D-isomer, unlike the L-isomer, is unable to prevent hepatic injury or stimulate glutathione biosynthesis. The L-isomer is able to increase liver glutathione 3 times compared to control (63).

The effectiveness of NAC is believed to be due to its ability to increase tissue cysteine and elevate glutathione concentrations after the hepatic glutathione pool has been depleted by paracetamol (64). In a prospective clinical study of fifteen patients, Prescott and colleagues considered NAC to be the antidote of choice for paracetamol overdose as it is comparatively well tolerated and was shown to prevent paracetamol hepatotoxicity (65). A subsequent retrospective study involving 62 paracetamol poisoned-patients treated with NAC within 8 hours after paracetamol ingestion showed there were fewer patients with liver injury, renal impairment, and death, as compared with supportive therapy in historical controls (66). NAC has since been used successfully to prevent hepatotoxicity after paracetamol overdose for more than 40 years (61).

1.3.3. Oral and intravenous N-acetylcysteine

Both the intravenous and oral routes of NAC have been commercially available since the drug was first patented in 1960. The IV therapy was used in studies of paracetamol poisoning treatment in Europe, Canada, and Australia since the 1970s, whereas only the oral route was used in the United States for management of paracetamol toxicity from 1970 until 2004 (65, 67). The comparative efficacy of the oral and intravenous regimens was unclear initially. Although some believe that the oral therapy is superior to IV NAC because the dose and duration of therapy is greater and longer than the IV regimen(68), a systematic review and meta-analysis found that the proportion of patients developing hepatotoxicity were 13.2% and 12.6% for IV and oral, respectively(69). Therefore, oral and intravenous NAC appear to be equally effective in prevention of liver damage. The oral route is inappropriate for some patients for example those with nausea and vomiting, which are commonly seen in poisoned patients. Another disadvantage of using oral NAC is alteration of absorption by other drugs, for example, anticholinergic and narcotic drugs ingested in combination with paracetamol inhibit gastric emptying hence delaying the rate of NAC absorption reducing its efficacy in preventing liver damage(70). On the other hand, some researchers claim that delay in starting therapy with NAC is the principal reason of liver failure in patients suffering with paracetamol overdose(71). The risk of liver damage dramatically increases when NAC is started beyond 10 hours of ingestion of a paracetamol toxic dose. Hepatotoxicity developed in 6.1% and 26% of poisoned patients treated with oral

NAC dose within 10 hours and within 10 to 24 hours after ingestion, respectively(67). All studies(71) that compare different regimens and route of N-acetylcysteine conclude that starting N-acetylcysteine within the first 10 hours post paracetamol overdose is highly effective in prevention of liver damage regardless of the route, dose, and duration of therapy.

1.4. Treatment approach

1.4.1. Clinical evaluation for paracetamol toxicity

Clinical manifestation

There are no specific symptoms of paracetamol overdose in the early stages of toxicity.

The clinical presentation can be classified into four stages, depending on the time from ingestion(58, 72).

Stage 1: 0-24 hours from ingestion. The patient is usually asymptomatic or may have some non-specific symptoms of nausea, vomiting, malaise, lethargy and diaphoresis. Liver function tests remain normal in this stage, except for massive overdoses where the liver enzymes might be elevated in 8 to 12 hours or early lactic acidosis may occur(73).

Stage 2: 24-72 hours from ingestion. It is a latent period where patients may appear to improve clinically but increased liver transaminases (ALT, AST) can be detected at this stage. More serious cases might have right upper quadrant pain with hepatomegaly, prothrombin time (PT) prolongation, and renal function impairment.

Stage 3: 72-96 hours from ingestion. Symptoms reappear including gastrointestinal (GI) symptoms, and these are associated with marked elevation of liver enzymes (ALT, AST) to greater than 1000 IU/L, with marked and increasing prolongation of PT. Poor prognostic signs including jaundice, encephalopathy, metabolic acidosis, and coma.

Stage 4: Days 4-14 (40, 72). In those who survive this is the recovery phase as signs and symptoms of hepatic damage gradually resolve.

Paracetamol nomogram

The decision whether a patient taking a paracetamol overdose requires treatment is dependent on the blood paracetamol level at least 4 hours post overdose ingestion using the Rumack-Matthew nomogram.

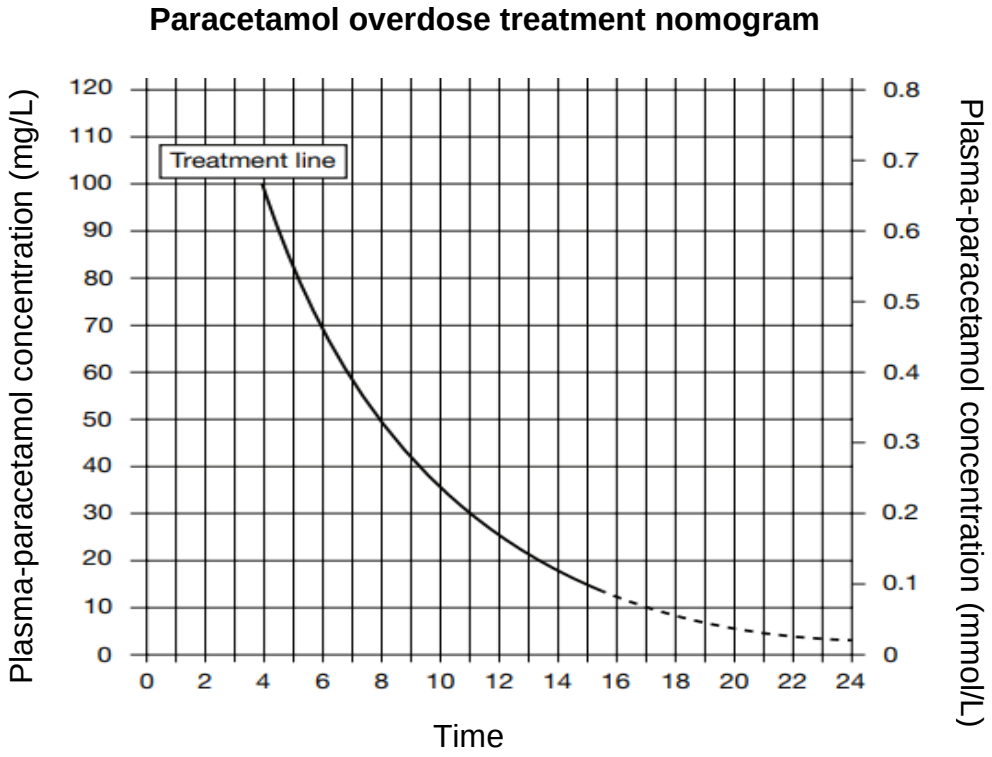


Figure 1-4: Paracetamol Treatment Nomogram in the UK(1)

The nomogram was devised (Figure 1-4) by Henry Matthew, head of the Royal Infirmary of Edinburgh Poisons Unit (Ward 3) in 1971. It is based on patients with acute paracetamol poisoning (74) and is used by clinicians to predict the risk of acute liver injury following acute paracetamol overdose and determine the need for treatment with acetylcysteine (75, 76). In the original UK nomogram, the risk of liver necrosis was considered high enough to warrant therapy if the plasma concentration was above a line beginning at 200 mg/l at 4 hours (the 200-line) but a lower treatment line beginning at 100 mg/l at 4 hours (the 100-line) was used in patients with risk factors for paracetamol-induced hepatotoxicity. In September 2012, the Commission on Human Medicines recommended the use of the 100-line in all patients regardless of the presence of risk factors in the UK. However, in the

US and Australia, the treatment line is defined as a line starting at a paracetamol concentration at 150 mg/l at 4 hours (the 150-line) (77). The nomogram is only applicable for single acute overdose, between 4 hours post ingestion up to 24 hours. The nomogram is not useful when the time of ingestion is unknown, before 4 hours has elapsed since overdose, beyond 24 hours after overdose, in staggered overdoses or in chronic therapeutic excess (74).

1.4.2. National Poisons Information Service (NPIS) guidelines on management of paracetamol overdose

The most recent guidelines on paracetamol overdose management by NPIS was updated on TOXBASE in October 2021.

The management is dependent on the dose pattern and time of ingestion. As a part of assessment, it is important to identify the appropriate type of paracetamol overdose based on NPIS definitions (**Table 1-1**). The decision to start treatment is based on the assessment of toxicity and blood results when available (**Figure 1-5**). The decision whether to start, continue or stop NAC is based on results of blood samples and clinical manifestations (**Table 1-2**) (26).

Blood measurement

All patients who require bloods should have the following taken (as per TOXBASE guidance):

- Full blood count (FBC), Urea and electrolytes (U+E), Liver function tests (LFT), Clotting, paracetamol level, and venous blood gas (including pH, glucose, and bicarbonate)
- Paracetamol levels are uninterpretable if samples are taken less than 4 hours post ingestion.

NAPQI-protein adducts can be detected as a biomarker, which can be detected in paracetamol hepatotoxicity, but the test is not widely available or used as part of standard clinical practice at this time.

Table 1-1: Types of paracetamol overdose

Dose Pattern	Definition	NAC indication
Single Acute	**Ingested overdose *over one hour or less*, in the context of self-harm:** • Dose ≥75 mg/kg for adult and children 6 years or older. • Dose ≥150 mg/kg (or the amount of overdose is uncertain) for children less than 6 years old.	**Any of:** • Plasma paracetamol concentration is above the at-risk line on the nomogram. • ALT above the upper limit of normal, unless patients with a chronically elevated ALT. • Symptomatic patients. • Time of ingestion is uncertain.
Staggered	**Ingested overdose *over more than one hour*, in the context of self-harm:** • Dose ≥150 mg/kg in any 24-hour period for both adult and children	All patients who have ingested a staggered overdose
Therapeutic excess	**Ingested overdose *greater than the licensed daily dose usually over more than 24 hours*, without self-harm intent.**	**Any of:** • Symptomatic patients • Dose greater than a licensed dose and ≥75 mg/kg in any 24-hour period for both adult and children • Dose greater than a licensed dose, and <75 mg/kg/24 h on each of the preceding 2 or more days.

Table 1-2: Criteria for Continuation or Discontinuation of Acetylcysteine (NAC) infusion

NAC administration:

Start or Continue if:

- ALT is above the upper limit of normal, OR
- INR is greater than 1.3 (in the absence of another cause, e.g. warfarin) OR
- Paracetamol concentration is detectable

Stop If:

- The paracetamol concentration is less than 10 mg/l, AND
- The ALT is within the normal range, AND
- The INR is 1.3 or less, AND
- The patient has no symptoms suggesting liver damage.

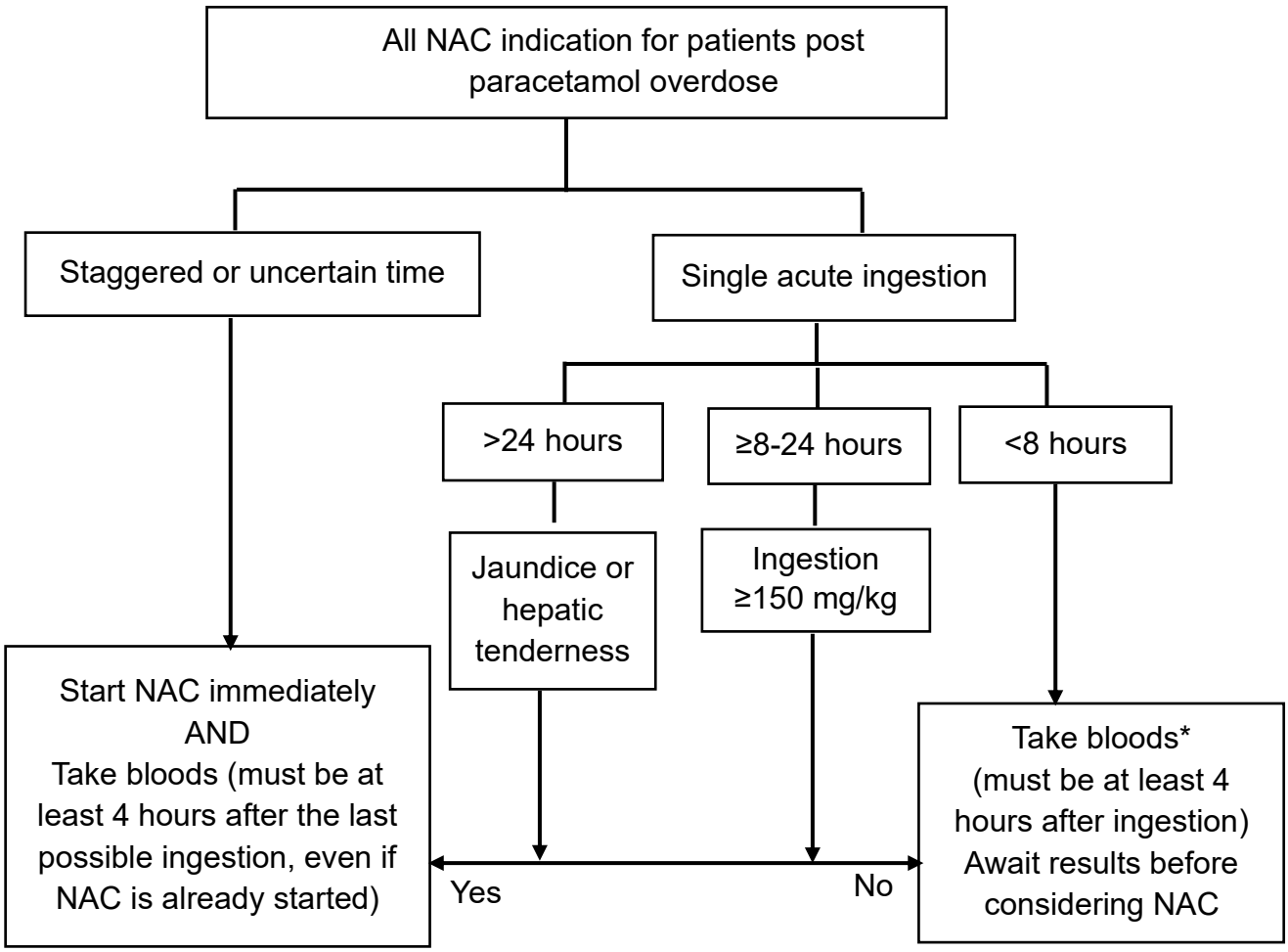


Figure 1-5: Flowchart to decide when to take bloods and whether to start N-Acetylcysteine (NAC)

1.4.3. Current acetylcysteine regimens for paracetamol overdose

Oral NAC

Dose and duration calculation

Bateman & Rumack described the basis for calculation of the oral NAC dose and duration. Used in the US until 2004 (78).

First, the toxic dose of paracetamol was estimated for an average human. The average paracetamol mercapturate excretion was 4% in 10 human volunteers to estimate the proportion of glutathione (mercapturic acid) conjugates after a single paracetamol dose (900 mg to 1800 mg). Based on the assumptions that 1 mmol of glutathione depletion required 1 mmol of acetylcysteine replacement, 4 mmol/l total glutathione content in human liver, and 70% glutathione depletion is needed to develop hepatic necrosis, the toxic dose of paracetamol was estimated as 15g or more as follows:

- 70% depletion of 4 mmol/l of endogenous glutathione in a 1.5 L liver is 4.2 mmol (70%× 4 ×1.5)
- 4.2 mmol, using the molecular weight of paracetamol of 151.2 is equivalent to 635 mg of paracetamol toxic metabolites
- As toxic metabolites represent 4% of toxic dose of paracetamol, 635mg of toxic metabolites result from a toxic dose of 15.9g (4% of 15.9 g).

For the oral NAC protocol, 4 hourly dosing was proposed based on a paracetamol half-life of 4h with the aim of replacing glutathione at the rate of 1 mmol/h (i.e 25% of the 4.2 mmol glutathione depletion per hour). The fractional rate of glutathione turnover is between 0.2 and 1.5 mmol/h. As the proportion of toxic metabolites (NAPQI) is expected to increase with increased dose, the turnover of glutathione has been estimated to be at least 1.5 mmol/h which together with the 1 mmol/h glutathione repletion required gave a target of 2.5 mmol/h glutathione, which for a 70 kg adult translates to 6 mg/kg/h oral NAC (2.5 ÷ 70 = 0.036 mmol/kg, 1 g NAC = 6.1 mmol). As a safety factor, a loading dose of 140 mg/kg followed by 70 mg/kg every 4 hours for 72 hours was used, based on paracetamol half-life of up to 12h in overdose.

The oral NAC protocol was used in the United States but has largely been replaced by intravenous acetylcysteine since 2004.

Standard 21-hour regimen (Three-bag regimen)

Intravenous (IV) N-acetylcysteine is now the first-line antidote treatment for paracetamol overdose. The original IV NAC regimen was designed by Prescott in 1977 in the UK(65). Initially, the regimen was over 20.25 hours with 15 minutes infusion time for the loading dose. This dosing regimen is arbitrary and was developed without any dose-ranging studies to establish a safe and effective dose (79) although the loading dose of 150 mg/kg is very similar to the 140 mg/kg oral NAC loading dose. The protocol duration was developed based on assumption of a paracetamol half-life of approximately 4 hours in therapeutic doses. The total duration of treatment was based on five half-lives for IV protocol- 20.25 hours including 0.25 hour of loading infusion(79, 80).

The administration of IV NAC causes NAARs occurring most often during the loading infusion and these are associated with the high initial concentrations of NAC (81). A multicentre, randomized, prospective study recommended modification of the NAC regimen suggesting identifying the maximum lowest effective concentration of NAC considering NAC disposition is not dose dependent. However, slowing the loading infusion rate from 15 minutes to 60 minutes did not show any significant difference in adverse events including infusion adverse reactions (NAARs)(82).

The loading dose was subsequently extended to 1 hour by the UK Commission on Human Medicines (CHM) in 2012, with the aim of reducing early infusion-related adverse reactions(83, 84). Since 2012, the standard regimen for paracetamol overdose treatment involves IV NAC of 300 mg/kg over 21 hours administered in three consecutive doses (**Table 1-3**) (26).

Modified regimens (Two-bag regimen)

1. **Short 12-hour regimen (known as SNAP) Regimen**

An alternative NAC regimen was developed for investigation in the Scottish and Newcastle Antiemetic Pre-treatment for paracetamol poisoning study (SNAP) (**Table 1-3**) (85) , involving a reduced loading infusion rate from 150 mg/kg/h to 50 mg/kg/h, and shortened duration from 21 hour to 12 h, but with the same total dose of 300 mg/kg. Although the SNAP regimen is described on TOXBASE (26), the primary clinical toxicology database of the NPIS for patients with previous

severe anaphylactoid reactions, it is unlicensed and not endorsed by the Medicines and Healthcare Products Regulatory Agency (MHRA), as the efficacy in regards to preventing hepatotoxicity is not fully established in all patterns of paracetamol overdose.

2. Australia and New Zealand Regimen

A two-bag 20-h NAC regimen (**Table** 1-3) was initially implemented at the Monash Health Emergency Medicine Program in Victoria, Australia for 16 months in February 2014 (86). The two-bag regimen changed the loading dose infusion rate to 50 mg/kg/h, but the duration and total dose continued was the same as the standard regimen.

In March 2020, Australia and New Zealand updated their guidelines on the management of paracetamol poisoning to include a new recommendation for use of this two-bag acetylcysteine infusion regimen, as it is similar in efficacy but produces significantly fewer adverse reactions compared with the licensed three-bag regimen(87).

Table 1-3: Intravenous Acetylcysteine (NAC) treatment regimens.

	Standard regimen (3-bag)	**SNAP regimen (2-bag)**	**Australia and New Zealand Regimen (2-bag)**
Duration	21 hours	12 hours	20 hours
Loading dose	150 mg/kg Infuse over 1 hour	100 mg/kg Infuse over 2 hours	200 mg/kg infuse over 4 h
Maintenance dose	50 mg/kg Infuse over 4 hours 100 mg/kg Infuse over 16 hours	200 mg/kg Infuse over 10 hours	100 mg/kg Infuse over 16 h

1.4.4. Problems with current Intravenous acetylcysteine protocol

The most commonly used licensed 21-hour regimen of intravenous acetylcysteine, which has been modified from the original 20.25 h regimen described by Prescott and colleagues, has some flaws(88, 89).

Non-allergic Anaphylactoid reactions (NAARs)

NAARs to NAC is similar to anaphylaxis but has a non-immunological mechanism (90) and does not require prior exposure to NAC. Symptoms are related to the higher NAC concentration rather than true non-dose-related anaphylaxis (91). Nausea, vomiting, abdominal pain and mild cutaneous reactions such as flushing and urticarial are the most common features while angioedema, bronchospasm and hypotension are rare but are life threatening. These reactions are frequently seen within the first few minutes of initiating the loading dose infusion, and up to 50% of patients have been reported to have anaphylactoid reactions within the first hour infusion of the standard protocol (88). The high loading dose (150 mg/kg) infused over 15 to 60 minutes is thought to be the predominant cause for anaphylactoid reactions.

Dosing delay

The complex regimen using three different doses with different infusion times- 150 mg/kg, 50 mg/kg, and 100 mg/kg over 1 hour, 4 hours, and 16 hours respectively increases the risk of medication errors, including delays between administration of the three infusions. An observational study in three university hospitals in England showed that there is significant delay between the 1st and 3rd infusion. In 68% of cases there was a delay of more than one hour, in 40% more than 2 hours, and about 20% by more than 3 hours delay time compared with time that ideally should have been administered. This study shows that in most patients, there can be significant delays to the administration of NAC (92). Although the impact of these delays has not been studied, it is possible that resulting sub-therapeutic NAC concentrations might increase the risk of hepatotoxicity (93).

Administration errors

A retrospective review of poisons centre records by the University of Maryland-Baltimore showed errors in 33% (74 out of 221) of patients given the conventional NAC regimen for paracetamol overdose. Of these 13.1 % was the frequency of

unnecessary administration, which was assessed to cost $500,000 annually (89). A prospective clinical study found errors in dose calculations in 5%, errors in drawing up NAC in 3%, and inadequate mixing of preparations in 9%. The authors found that the errors from dose calculations was within 10%, 20%, and 50% of the anticipated dose in 37%, 61% , and 2% of patients respectively (94).

1.5. Optimisation of acetylcysteine regimens

Over 40 years use of Prescott's original NAC regimen has showed that it is very effective in preventing fulminant hepatic failure after paracetamol poisoning if administered early. As the three-bag regimen is a complicated protocol, Prescott recommended that the regimen needed optimisation. Subsequently, studies have tried various regimens that aimed to minimize the infusion adverse reactions and administration errors, and to adjust total duration of treatment (81, 95).

1.5.1. Studies with aim to minimise infusion adverse reactions

Infusion adverse reactions have been shown to be lower using two-bag regimen compared to the standard 3-bag regimen.

The SNAP study, a double-blind, randomised controlled factorial trial performed in three hospitals in the UK over 2 years (2010- 2012), found that a simplified regimen (two-bag) with a slower loading infusion rate of 100 mg/kg over 2 hours (50 mg/kg/h) instead of 150 mg/kg over 15 minutes significantly reduced the incidence of infusion-related NAARs (96). The regimen was based on results of Monte Carlo simulation of acetylcysteine concentrations using pharmacokinetic data derived from a previous study(81). Assuming that severe NAARs were commonly seen at concentrations greater than 650 mg/l with the conventional regimen, the simulation data estimated the peak NAC concentration with the SNAP regimen would be between 150 mg/l to 650 mg/l in 99% of patients and therefore lead to a marked reduction in NAARs compared to standard regimen. The also study showed significant reduction in vomiting and need for anti-emetic rescue (36% vs 65%) and in the incidence of severe NAARs (5% vs 31%) with SNAP group compared to standard treatment, respectively(96).

Several studies thereafter tried different modified regimens with the aim of reducing the frequency of NAARs. Three recent studies using a 2-bag regimen with a

loading infusion of 50 mg/kg/h (Australian regimen) all showed substantially reduced NAARs compared to 3-bag regimen.

A retrospective cohort study over 7-year period (2010-2017) demonstrated that NAARs were less frequent in cases treated with this two-bag regimen (4.0%) compared to the three-bag regimen (15.4%) (97).

A prospective study was conducted at three emergency departments on 210 patients treated with a two-bag acetylcysteine therapy (200 mg/kg over 4h, followed by 100 mg/kg over 16h). The authors compared this regimen with a historical cohort treated with the three-bag regimen as control group. Both groups had similar mean reported ingested paracetamol dose by weight. The study demonstrated that the rate of NAARs was statistically significantly lower in the two-bag group (two-bag 4 % vs three-bag 10%, P=0.01). All cases that required temporary acetylcysteine discontinuation and antihistamine treatment were from the 3-bag group while none of the 2-bag group needed any treatment interruptions because of adverse effects (98).

McNulty et al. conducted a prospective study comparing a two-bag regimen (200 mg/kg over 4 h (50 mg/kg/h) and 100 mg/kg over 16h), using a historical cohort of people treated with standard therapy and reported a 9% reduction in NAARs with the shortened protocol (91).

However, these three studies did not report significant reductions in gastrointestinal reactions such as nausea or vomiting with the 2-bag regimen.

1.5.2. Studies with aim to minimise administration errors

Errors associated with intravenous acetylcysteine of simplified regimen is still similar to the conventional regimen in a single centre retrospective study (99); but there are few studies directly comparing administration errors between various regimens (94, 100).

A single teaching institution for Washington University School of Medicine evaluated a simplified single bag NAC dosing regimen with a fixed NAC concentration using an intelligent infusion device that can alter the infusion rate automatically, with delivery of 150 mg/kg as a loading dose for one hour and decreasing to 14 mg/kg/h for 20 hours as a maintenance dose, the total dose was 430 mg/kg. This, however, did not show any significant difference in the overall error rate between the FDA-approved (3-bag) and the study regimen (60% vs 38%,

respectively), (p = 0.383, OR = 1.53, 95% CI 0.52 to 4.57) (99), but the study regimen reduced the rate of interruptions longer than 60 minutes. Therefore, reducing the number of infusions might help in minimising delays between infusions.

A retrospective analysis estimating prescription errors in the 21h three-bag regimen, and a two-bag regimen (200 mg/kg over 4 h followed by 100 mg/kg over 16 h) showed that the incidence of errors was not statistically significant between the two groups (p=0.35) (80).

Both aforementioned studies are not adequately powered for the outcome of medication errors and limitations included retrospective analysis, small number of patients and conducted in a single centre. Even though the benefit of modified therapy in reducing dosing errors has been insufficiently measured, larger clinical studies are required to measure benefit of the two-bag regimen on incidence of errors.

1.5.3. Studies with aim to adjust duration of treatment

In recent studies, there have been attempts to reduce the duration of NAC therapy, aiming to have a simpler and shorter regimen which is as effective as the traditional one (96, 101). A 20-hour protocol was based on five half-lives on the assumption that this would be adequate for disappearance of toxic metabolites of paracetamol from the body (79). However, the half-life of patients without hepatic impairment is shorter than those with hepatotoxicity ranging from 1.5 to 2.5 hours (102) in those with no liver injury, so 20 hours therapy may be unwarranted in those patients. A large proportion of patients who receive the traditional regimen do not develop hepatotoxicity with an incidence of hepatotoxicity lower than 8% in the majority of clinical studies (82, 93), particularly when intravenous NAC is initiated within 8 hours post overdose. Hence, it is possible that most patients will be treated successfully with a shorter regimen (81, 96). There may be concern about the effectiveness of a shorter regimen in some patients e.g those who present late or take large overdoses. On the other hand, the patients who are at high risk of liver injury might require extra bags when, for example the total NAC dose may be insufficient for treatment of a massive paracetamol overdose. Cairney et al found that patients who ingest large doses of paracetamol often require treatment with acetylcysteine beyond 21 hours, suggesting that the 21 hour duration might be

insufficient if there is ongoing formation of toxic metabolites (103). A regimen which can be used flexibly to deliver the 300 mg/kg total dose in a shorter period of time for most patients and a higher dose for at-risk patients would be beneficial.

1.6. Aim of the study:

The aim of this study is to evaluate a modified acetylcysteine regimen (SNAP) that aim to minimize adverse reactions, simplify administration to reduce errors and shorten the total duration of therapy, and develop a new simpler protocol and clinical pathway to facilitate implementation in clinical practice.

1.7. Objectives:

1. Simulate the pharmacokinetic profile of NAC of different modified regimens to compare the highest initial concentration, and steady state concentration of SNAP with standard 21h regimen.
2. Compare clinical outcomes of liver toxicity between simplified (SNAP) and conventional regimen post paracetamol overdose.
3. Analyse the relationship between liver toxicity with time from ingestion to starting NAC to evaluate the efficacy SNAP in all risk group of patients.
4. Analyse the effect of the SNAP regimen on the INR.
5. Develop a simple clinical decision rule for predicting safe discharge of patients at the end of the 12h SNAP regimen.

CHAPTER 2

PHARMACOKINETIC SIMULATION

Chapter 2 : Pharmacokinetic simulation of different acetylcysteine regimens

2.1. Introduction

2.1.1. Pharmacokinetic models

Pharmacokinetics provides scientific information about the body's handling of a drug which can be used to design an effective dosing regimen for patients. The processes of absorption, distribution, metabolism, and excretion can be described experimentally by calculating clinical pharmacokinetic parameters after determination of the plasma drug concentration versus time profile(104). This can then be used to determine an effective and safe dosage regimen if the minimum effective dose and maximum tolerated dose are known.

Drug handling is a complex process with the drug distributing from plasma to different organs and tissues within the body. (105). The rate constant represents the velocity of that process. The order of reaction refers to how the rate of the process depends on the drug concentration. The two basic kinetic models are zero and first order.

In zero order kinetics, the elimination rate is constant and independent of drug concentration in the body whereas with first order kinetics, the elimination rate is directly proportional to the drug concentration in the body(106). A hypothetical way to characterise the body's handling of the drug is to apply compartment models (**Figure 2-1**) to estimate the distribution and time course of the drug in different tissues/organs (compartments). Compartment models can be a simple one-compartment model (when the drug is assumed to be distributed equally throughout the body) to more complex multi-compartmental models (when the drug is assumed to partition between plasma and other organs/tissues). The concept behind such models is to construct the body into organs and tissues and to assume the drug is equally distributed in organs and tissues. The compartments are often defined as a central compartment, which consist of organs with high perfusion such as blood, heart, liver, and kidney, or peripheral compartment, which has lower perfusion; such as fat or muscle tissue. In a one-compartment model, the drug is distributed immediately and equally to all body parts, whereas in a two

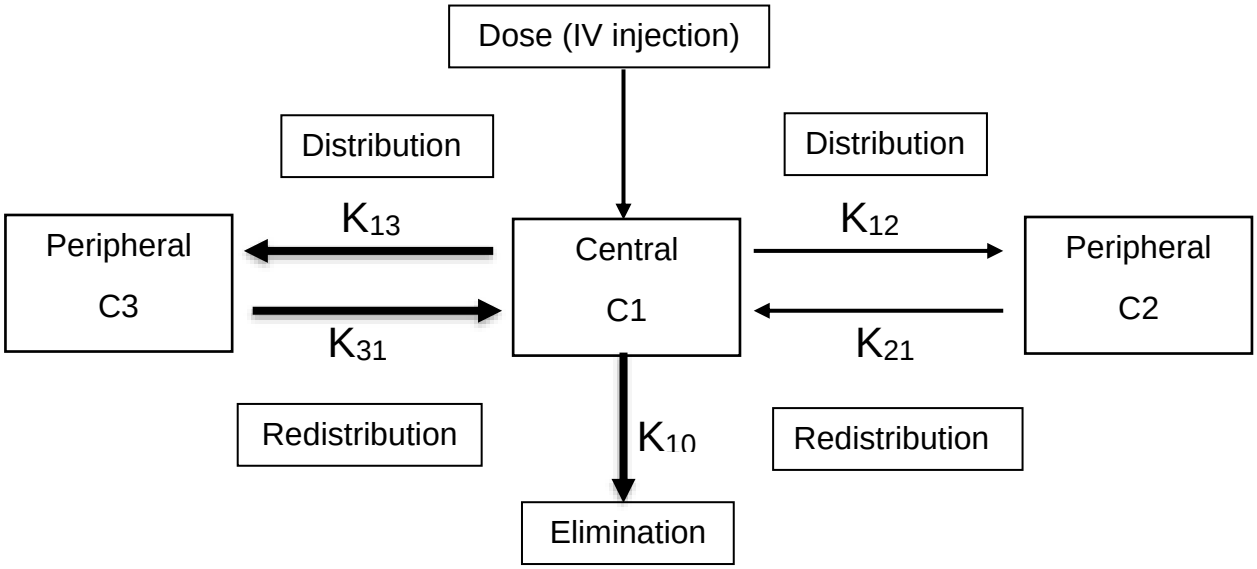


Figure 2-1: N-Acetylcysteine compartment model with first-order elimination. C1 represents concentrations of drug in the central compartmen (including plasma), and C2, and C3 represent concentrations of drug in peripheral compartment. k10 represents elimination rate constant from central compartment. k12, k21, k13, k31 represent the fractional rate constants for distribution, redistribution.

compartment model, the drug is distributed rapidly to blood and high perfusion organs (central compartment), then more slowly redistributed to other body tissues (peripheral compartment). The drug continues to move back and forth between two compartments until an equilibrium is maintained. In a three compartment model, there is a central compartment and two peripheral compartments (105).

In summary, pharmacokinetic modelling provides a simple mathematical approach to characterise the transit of drug in the body which can be used to determine an optimal dosage regimen.

2.1.2. Pharmacokinetic parameters:

Clearance

Clearance for a drug is the ability of the body to excrete the drug, which can be expressed as theoretical ‘volume’ of plasma that is cleared of drug per unit of time. The elimination process is primarily by renal or hepatic elimination or in combination, but other processes can be involved such as elimination or metabolism at sites other than the liver (lung, saliva, skin, or other tissues).

Therefore, the total clearance of a drug is the sum of the clearance by various organs as this equation defines:

$CL_{Total} = CL_{renal} + CL_{hepatic} + CL_{other}$.

Clearance can also be defined: $CL = k \times V_d$, k is first order elimination rate constant(106, 107). The clearance of a drug is constant if the drug is eliminated by first order kinetics, but it is not constant when kinetics are zero order.

Volume of distribution

The volume of distribution (V_d) for a drug is the apparent volume in which the drug appears to be dissolved in after it reaches a state of equilibrium in the body. The apparent distribution can be measured from the drug dose (X) divided by the plasma concentration (C_p): $V_d = \frac{X}{Cp}$

A high apparent volume distribution indicates that most of the drug moves into various organ systems, while small apparent distribution means that a higher proportion of the drug remains in the plasma and does not go effectively into various organ systems(106, 107). It should be noted, however, that distribution to other organs will not be uniform and depends on other factors including lipid solubility and active transport mechanisms.

Half-life

The half-life ($t_{1/2}$) is the time it takes for the plasma concentration to decrease by 50% as a result of elimination.

In a 1-compartment model, the relationship of volume and clearance to $t_{1/2}$ is given by: $t_{1/2} = (0.693). \frac{V}{CL}$. (107)

AUC (Area Under the curve)

It reflects the actual body exposure to drug after administration of a dose of the drug and is expressed in mg*h/L. This area under the curve is dependent on the rate of elimination of the drug from the body and the dose administered. AUC can be calculated by the trapezoidal rule, which involves dividing the plasma concentration-time profile into several trapezoids and calculating the AUC by adding the area of these trapezoids. It can also be calculated from the dose divided by the apparent clearance (CL): $AUC = \frac{Dose}{CL}$.(108)

C_{MAX}

C_{max} refers to the maximum concentration that a drug achieves in blood or plasma after the drug has been administrated and prior to the administration of a second dose. T_{max} is the term used in pharmacokinetics to describe the time at which the C_{max} is observed. They could be used to characterize the properties of different formulations in the same subject. Short term drug side effects are most likely to occur at or near the C_{max} whereas the therapeutic effect of drug with sustained duration of action usually occurs at concentrations slightly above the $C_{min,}$ which is the opposite of C_{max}, and refers to minimum blood plasma concentration reached by a drug during the time interval between administration of two doses (108).

2.1.3. Simulation

Pharmacokinetic simulation uses software which allows the input of published clinical population pharmacokinetic data of the drug to generate theoretical pharmacokinetic drug profiles for 100-5000 hypothetical patients.

A simulation based on published 3-compartmental model of NAC on 24 healthy subjects by Brown et al. (109, 110) was used to the predict time course of drug concentration in relevant compartments (104, 111).

2.1.4. Pharmacokinetics of NAC

NAC assay

Although NAC was shown to be effective as a mucolytic in the treatment of bronchitis and protective against chemotherapy toxicity, there are few studies of the pharmacokinetics of intravenous NAC due to difficulty in assaying NAC and its various derivatives(112). NAC is thiol group and is found in plasma as a free, a reduced from, and various oxidized forms(113). The oxidised NAC disulphides exist either as a dimer or mixed with free thiol groups such as cysteine, glutathione, or proteins such as albumin. Plasma non-protein-bound N-acetylcysteine components (either total NAC or the reduced from) are considered for pharmacokinetic assessment. In pharmacokinetic studies, the reduced form was

sometimes considered as parent drug and all other forms as metabolites, or the total NAC (reduced and oxidized form) as parent drug(114, 115).

NAC distribution:

Although NAC disposition and clearance are not fully understood, it is clear that NAC is distributed and eliminated from organs other than liver as the plasma concentration is not elevated and clearance is not reduced in the presence of liver impairment. An important factor in NAC distribution is the thiol group, because this binds to sulfhydryl-containing molecules in plasma, tissue, or organs. McLellan et.al showed using autoradiography that radiolabelled NAC was observed in the majority of body organs and tissues, but primarily in the liver, kidney and gastrointestinal tract. NAC can also be found in heart, lung, and muscle, but at very low concentrations, while radioactive NAC was not detected in brain or spinal cord (62). The authors measured the hepatic uptake of intravenous radiolabelled NAC at a dose of 320 mg/kg. Liver uptake of radiolabelled NAC starts within 15 minutes of injection, with maximum time of peak at 45 minutes, then the concentration declined gradually over 5h. Available data about NAC disposition and distribution in different body organs are extremely limited.

2.1.5. Pharmacokinetic parameters of NAC

Intravenous NAC

Accurate analytical methods to measure NAC in plasma and urine were not available until the drug had been used in clinical practice for more than 20 years. In 1986, Borgstrom et al published the first basic pharmacokinetic data of intravenous and oral NAC using a chromatography analysis method to detect total de-proteinated NAC in the plasma of 10 healthy volunteer subjects. After administering intravenous NAC 600 mg (3676 mmol) over 5 minutes and collecting the urine for first 12 hours from intake, they found that the maximum NAC concentration was 300 mmol/l and the mean endogenous proportion of NAC excreted in the urine was only 10% (116). The volume of distribution at steady state was 0.337±0.027 L/kg, elimination half-life 2.27±0.32 h and NAC was undetectable in plasma after 12 h of administration. The total clearance in this study was 0.21 L/h/kg, renal clearance was 0.058 L/h/kg, so 70% of total clearance was non-renal.

Published pharmacokinetic data (110) of NAC are limited and the reported pharmacokinetics parameters vary from one study to another based on number of differences:

- **Measure different forms of NAC in plasma**

NAC analysis is complicated as it exists in different forms in plasma: free or bound to protein either in the form of reduced, oxidized, or mixed with other thiol or sulfhydryl group. The protein bound form represented 50% of total NAC assayed in plasma(114).

Olsson et al conducted a basic pharmacokinetic study of 12 healthy subjects in 1988 for both total NAC and reduced form. Even though the de-proteinated form of NAC is around 50% of total drug, the authors found that pharmacokinetics parameters of total NAC is similar to de-proteinated total NAC in Borgstrom et al study. The volume of distribution and total clearance of reduced NAC after given 200 mg/kg intravenous bolus NAC are 0.47 L/kg , and 0.19 L/h/kg, for volume distribution, and total clearance, respectively(117).

- **Measure IV NAC during exercise**

Another pharmacokinetic study was conducted using a three-compartment model in 24 healthy male volunteers after administration of 2 consecutive NAC infusions: 125 mg/kg/h for 15 minutes followed by 25 mg/kg/h for 35 minutes at rest. The infusion was continued during cycling exercise and ended when the subjects stopped exercising. The whole-body clearance of total NAC was reduced by 23% during exercise to 0.164 L/kg/h while the central volume distribution did not significantly change after exercise (0.037 L/kg). The mean plasma concentration of NAC was 205.1 mg/l with the peak concentration of 310.5 mg/l at the end of 20 minutes, and steady state concentration was 150 mg/l. The authors suggested that a concentration of 100 mg/l of NAC is sufficient to provide pharmacological action without causing severe adverse reactions (110).

This 3-compartmental pharmacokinetic model of intravenous NAC described in this study has been used for pharmacokinetic simulation of alternative NAC regimens

in this chapter as the 2-infusion used more closely reflect the intravenous NAC regimen used for paracetamol overdose.

- **Patients with Liver impairment**

In 1988, Prescott and colleagues studied the kinetics and disposition of NAC in 17 patients receiving the 3-bag intravenous NAC regimen. 12 of these had mild (ALT< 500) and 5 had severe liver damage (ALT> 1000). The mean maximum plasma concentration of total N-acetylcysteine after the first infusion (150 mg/kg over 15 minutes) was 554 mg/l; subsequently the NAC concentration gradually decreased to a mean steady state plasma concentration of 33.4 mg/l. At the end of the third infusion, the NAC concentration fell with a mean terminal elimination half-life of 5.7h. A 2-compartmental model was used in this study, but the pharmacokinetic parameters were reported as for a non-compartmental model: the mean steady-state volume of distribution, and total body clearance of total NAC were 536 ml/kg, and 3.18 ml/min/kg, respectively. Interestingly, unlike paracetamol, the pharmacokinetics of NAC did not alter in the presence of hepatic damage. i.e. NAC clearance was not reduced and plasma NAC concentration did not increase, and NAC elimination half-life was not prolonged in patients with liver damage(81).

In contrast, Jones et al, (1997), reported a pharmacokinetic study of 9 patients with chronic liver disease (cirrhosis) and 6 healthy volunteers. The serum NAC concentration after administration of a 600 mg bolus of intravenous NAC was significantly different between the two groups. The total body clearance of NAC was significantly reduced in patients with liver impairment who developed mean plasma NAC concentrations three times higher than those in the healthy controls; nevertheless, no patients developed NAARs. Total clearance was 4.5 l/h vs 6.5 l/h, t ½ was 2.7 h vs 4.9 h, and area under the curve was 152 vs 93.9 mg/l/h in control and cirrhotic groups respectively(118). The study suggested that the liver plays an essential role in NAC clearance and recommended to reconsider the current dose of NAC in cirrhotic patients.

- **Patients on haemodialysis**

A pharmacokinetic study of NAC was performed in chronically haemodialysed patients with end-stage renal disease to assess the safety of administering a higher dose NAC during dialysis sessions. The study was performed on 12 dialysis subjects and given 2 g NAC infusion during the first 3 hours of dialysis for six dialysis sessions. The plasma NAC concentration in patients with end stage renal disease reached steady state after the fourth dialysis session, with concentrations increasing towards this over the first three sessions. The study indicated that even though NAC accumulated in the initial three dialysis, the concentration of NAC reached steady state without further accumulation thereafter. Initially, the dialytic clearance was 0.019 l/h/kg, which is much lower than in patients without renal disease (0.11 l/h/kg), but dialytic clearance later was similar to healthy subjects (5.66 l/h versus 5.27 l/h). (119).

Oral NAC

The oral formulation in general has very low bioavailability, which is probably due to metabolism during its first passage in the gut wall and liver. The bioavailability is not greater than 10% of total drug ingestion, which indicate that oral dose should be higher than intravenous dose. However, due to the fast oral NAC metabolism in the liver, where the NAC needed for glutathione synthesis, oral NAC is still effective for treatment paracetamol toxicity in spite of low systemic bioavailability(116).

Novel thiol derivatives were developed to improve bioavailability. NAC amide (NACA) was synthesised in 1967 with similar antioxidant properties to NAC. He et al first reported pharmacokinetics and bioavailability of NACA in vivo. They found that the bioavailability of oral NACA is significantly higher than NAC (67% and 15%, respectively). The glutathione-repleting capacity was three to four-fold higher in NACA compared to NAC (120). The current view is that oral NACA is a promising antidote for paracetamol toxicity.

2.1.6. Recent intravenous NAC protocol:

In last two decades, a number of different NAC regimens have been studied to improve on the Prescott's original regimen (65). Some of these increased the total dose used, while most aimed to simplify and minimise the side effects of NAC administered using the standard protocol. The Prescott regimen uses a total dose

of 300 mg/kg NAC, based on estimated paracetamol absorption and turnover rate of glutathione. More recently a 400 mg/kg total dose has been suggested by Australian studies for patients who take massive paracetamol overdoses e.g >40g (87, 121). Abbreviated regimens involving two infusions, sometimes shortening the total duration of therapy have been associated with lower rates of infusion-related adverse reactions. The most common modified regimens that have been implemented into routine clinical practice are the Australian 2-bag protocol (98) (200 mg/kg over 4h as an initial dose followed by 100 mg/kg over 16 h as a maintenance dose), double dose Australian regimen (200 mg/kg over 4h as an initial dose followed by 200 mg/kg over 16 h as a second dose), and the SNAP 2-bag protocol(122) (100 mg/kg over 2h followed by 200 mg/kg over 10 hours) (**Table 2-1**)

Both Australian regimens were recommended in the recently updated Australian and New Zealand guideline for the management of paracetamol poisoning in 2020. The SNAP regimen has been implemented with local audit of outcomes since 2016 in three UK hospitals - St Thomas Hospital in London, Royal Infirmary of Edinburgh, and Royal Victoria Infirmary of Newcastle.

Table 2-1: The most common acetylcysteine regimens for treatment of paracetamol overdose

Regimen	Total dose	Duration	1st dose	2nd dose	3rd dose
Standard	300mg/kg	21hrs	150mg/kg over 1h	50mg/kg over 4h	100mg/kg over 16h
Australian	300mg/kg	21hrs	200mg/kg over 4h	100mg/kg over 16h	-
Double dose-Australian	400mg/kg	21hrs	200mg/kg over 4h	200mg/kg over 16h	-
SNAP	300mg/kg	12hrs	100mg/kg over 2h	200mg/kg over 10h	-

2.1.7. Application of pharmacokinetic modelling:

As an alternative to performing a full pharmacokinetic study with plasma concentration measurement, pharmacokinetic simulation can be used to predict NAC concentration of various NAC regimens used in clinical practice. Specifically, the modelling was used to predict the initial peak concentration, steady state plasma NAC concentration, and concentrations with time after infusion cessation.

A Monte Carlo method was used to simulate estimated NAC concentrations using the SNAP regimen based on a 1-compartment pharmacokinetic model. This estimated that 99% of patients were expected to have peak NAC concentrations in the range from 150 mg/l to 650 mg/l and mean NAC concentrations of 30 mg/l at 20 h post infusion. Assuming that NAARs are concentration-related and occur when NAC plasma concentration exceed 150 mg/l, the SNAP regimen would be expected to reduce the incidence of NAARs significantly. Assuming that the minimum steady state plasma concentration of 30 mg/l achieved with the 21 h regimen is required for efficacy, the SNAP regimen was expected to be as effective; hence, simulation can be used to find an optimal regimen for further clinical study(85).

Chiew et al. simulated seven published regimens of acetylcysteine using three compartment model to compare the peak NAC concentration, area under the curve, and the plasma concentration–time curve. The authors found the slowing the loading dose reduced the peak NAC concentration. The mean peak acetylcysteine concentrations were highest (1200 mg/l) with a loading dose of 150 mg/kg over 15 minutes, but were lower if the initial infusion was slower: 560 mg/l with 150 mg/l over 60 minutes, 260 mg/l with 200 mg/kg over 4 h, and 225 mg/l with 100 mg/kg over 2 h. Clinical studies using the slower loading dose and lower peak NAC concentration demonstrated lower adverse reaction rates. The mean NAC concentration 20 h after initiation of NAC infusion was lowest with the 12 h modified regimen at 18 mg/l, compared to 40 mg/l in all 20 h duration regimens but it is unclear what the minimum steady state NAC concentration at 20 h is in relation to efficacy. The authors asserted that the majority of paracetamol overdose cases do not require such large or prolonged dose of NAC (111).

Wong et al. modelled different regimens of intravenous NAC(101), including extended treatment with an additional infusion of NAC for patients who need extra treatment after the 21 h NAC infusion. They compared the standard three-bag 21 h regimen (150 mg/kg over 1 h, 50 mg/kg over 4 h, 100 mg/kg over 16 h), two-bag 20h regimen (200 mg/kg over 4 h, 100 mg/kg over 16 h), and abbreviated two-bag 12 h regimen (200 mg/kg over 4 h, 50 mg/kg over 8 h). The study found the maximum concentration following intravenous NAC were 567mg/l at 1h with the three-bag regimen, and 261mg/l at 4 h for both the two-bag regimen and the abbreviated regimen. At 20 h after initiation of the NAC infusion, the concentration was similar using the three-bag and two-bag regimens (38 mg/l) and much lower (2.2 mg/l) using the 12 h regimen. The concentration at the end of 12 h infusion was very similar in all three regimens, which is above 40 mg/l. The study believed that 12 h abbreviated regimen might be appropriate for patient with low risk of liver injury post paracetamol overdose as the NAC can be detectable up to 8 hours after cessation (98).

All these pharmacokinetic simulation studies provide justification for altering the conventional 21h NAC regimen to reduce adverse reactions. It is clear from both studies that slower initial infusion in two-bag regimen and SNAP regimen had lower peak concentration.

Whilst the 12 h SNAP regimen (100 mg/kg over 2 h, 200 mg/kg over 10 h) was shown to reduce the rate of NAARs, it was not clear at the end of the study how the NAC infusion should be administered at the end of 12h in those patients who had abnormal liver function tests or detectable paracetamol concentrations.

2.1.8. Rationale of SNAP protocol:

A shorter duration therapy while maintaining safety and effectiveness would be a major advantage for acetylcysteine protocols. The majority of paracetamol-poisoned patients presenting to hospital do not develop hepatotoxicity, even in those where therapy is indicated on the basis of paracetamol concentrations. Thus, it is likely that a large number of patients receive excessive doses of NAC or are treated for longer than required, extending their duration of hospital stay. In those who develop hepatotoxicity or in patients who take massive paracetamol overdoses, NAC would need to be continued.

The main reasons for using SNAP regimen are: first, as NAARs are thought to correspond to peak concentrations of NAC, the SNAP regimen would lead to lower adverse reactions compared the standard regimen; second, SNAP is a simpler regimen and may lead to fewer medication errors; finally, the 12-hour duration of SNAP can reduce the duration of hospital stay compared to 21-h regimen, which requires over 24 hours for the majority of patients.

Pharmacokinetics simulation objectives:

The purposes of pharmacokinetic modelling are:

- To predict the peak and steady-state intravenous NAC concentration using the SNAP regimen with different infusions after the 12h.
- To compare the peak and steady state NAC concentration with SNAP versus the standard and Australian 2-bag regimen.
- To simulate the impact on NAC concentration of different time delays between 1st and 2nd infusion.

2.2. Methods

2.2.1. Simulation

The pharmacokinetic simulation was conducted using Accelera for Sandwich (A4S, version 12)(123) software to perform simulations with 1000 virtual patients with different intravenous NAC regimens.

The software involves around 12 different pk modules. All PK models were described using the model structure, the dosing regimen and the simulation time. The users can choose the correct model through an interactive window, which allows the input of the relevant model parameters. For defining the model structure, from ADVAN library (**Figure 2-2**), we chose two compartment linear model with IV dosing (infusion) (ADVAN 3) and three compartment linear model with IV dosing (infusion) (ADVAN 11) for simulations of total and reduced NAC regimen. The second window is to choose the appropriate TRANS nomenclature for the desired parameterization, which is TRANS 4 in this simulation. After the model has been parameterized, the dosing regimen in term of number of doses and, for each dose, in term of dosing time, duration and amount were defined for each regimen

separately (**Figure 2-2**)(124). Once all information is available, the A4S Simulator generates the profile of plasma drug concentration versus time data for the selected model. To import a previously saved simulation PK profile for overlayed simulated NAC regimens on current simulation profile (Edit, overlay previously simulated PK).

Based on published population pharmacokinetic models, total NAC only was simulated using a 2-compartmental model (**Table 2-2**) (123, 125), and both total NAC and reduced NAC using a 3-compartment model (**Table 2-3**) (110).

The PK data using these simulations were used to describe peak and steady-state serum NAC concentrations over time for the three-bag 21h conventional regimen, two-bag Australian regimen, double dose two-bag Australian regimen, SNAP regimen(123).

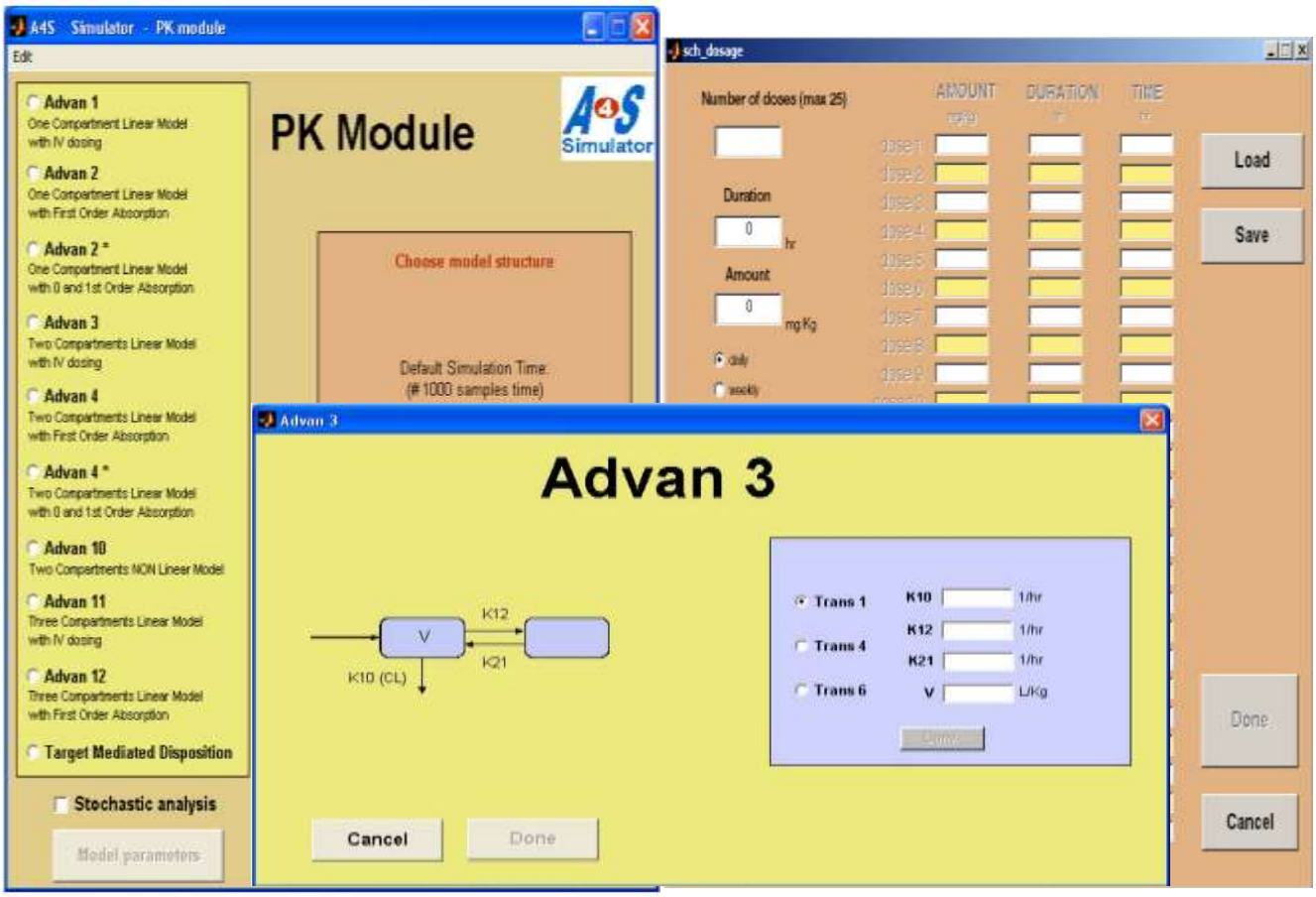


Figure 2-2: A4S Simulator user's interface. Window examples for setting ADVAN 3 model parameters, for the dosing regimen and the simulation time(124).

Table 2-2: Pharmacokinetics parameters of two compartment model

Model parameter	Total NAC	Reduced NAC
CL (whole-body clearance) (SD) L/hr/Kg	0.588643 ± 0.02	Not available
Q (inter-compartmental clearance (SD) L/hr/Kg	0.13081 ± 0.031	
V1 (central distribution volume) (SD) L/Kg	0.40878 ± 0.06	
V2 (peripheral distribution volume) (SD) L/Kg	0.327024 ± 0.03	

Table 2-3: Pharmacokinetics parameters of three compartment model

Model parameter	Total NAC	Reduced NAC
CL (whole-body clearance) (CV %) L/hr/Kg	0.164 (10.7)	0.58 (12.3)
Q2 (inter-compartmental clearance (CV %) L/hr/Kg	0.123 (23.9)	1.01 (46.2)
Q3 (inter-compartmental clearance) (CV %) L/hr/Kg	0.43 (10.9)	0.063 (19.5)
V1 (central distribution volume) (CV %) L/Kg	0.037 (31.2)	0.064 (44)
V2 (peripheral distribution volume) (CV %) L/Kg	0.21 (10.3)	0.125 (23.8)
V3 (peripheral distribution volume) (CV %) L/Kg	0.035 (21.8)	0.14 (16.8)

2.2.2. Clinical scenario

All patients were simulated had the same clinical scenario before starting NAC for treatment paracetamol overdose. It was expected that patients arrived at the hospital with paracetamol overdose and they were eligible for treatment with NAC according to UK National Poisons Information Service guidance as published on the TOXBASE database. All simulated patients had no relevant past medical

history or medical problems. It also was assumed that NAC treatment started once blood results were available. i.e. at least 4 h post overdose, and continued to the end of the modelled infusion, unless a simulated gap was introduced between the first and second infusions.

Exposure scenarios

- Comparison the peak and steady-state concentration of total and reduced NAC applying conventional and two-bag regimens and based on both two and three compartment models.
- Using different gap times between 1st and 2nd infusion and 2nd infusion and 3rd infusion of SNAP regimen and the impact of this on NAC concentration

2.3. Result:

The results of 1000 virtual patients' simulations of total and reduced NAC concentration versus time profile based on three, and two compartment model are summarized in Figure **2-3** and Figure 2-4.

The graphs demonstrate that the conventional regimen produces the highest peak concentrations, whether the simulation is based on a two or three compartment model or total or reduced form NAC. The mean peak concentrations of total NAC based on the three-compartment model are 560 mg/l, 225 mg/l, 260 mg/l and 260 mg/l for the conventional, SNAP, Australian, and double dose Australian regimens respectively (**Figure 2-5**). Compared to the total plasma NAC, peak concentrations of reduced NAC are lower for all simulated regimens. (Figure 2-4).

The SNAP regimen has the lowest peak concentration 225 mg/l, 70 mg/l, (Figure **2-3**) and 80 mg/l (Figure 2-4) when it is simulated based on total NAC (3-compartment, 2-compartment) and reduced NAC respectively. The peak concentration of SNAP regimen was 60% lower than for the conventional regimen. For both the Australian regimen and double dose Australian protocol, the highest initial concentrations were marginally higher than for the SNAP regimen in both compartmental models. Also, the simulation showed that the maximum concentration during the treatment cycle for both the conventional

and SNAP regimens were reached within the first hour of the initiation, while with both Australian regimens NAC concentration took at least 2 to 3 hours to reach its peak as a result of the time of duration infusion(**Figure 2-5**).

The predicted mean steady state concentrations of NAC were 40, 120, 40, 80 mg/l for standard, SNAP, Australian and double dose of Australian regimen respectively (**Figure 2-5**) indicating that the SNAP regimen achieves the highest steady-state concentration during the infusion, which may be important for efficacy in patients with sustained elevated paracetamol concentrations such as after massive overdose or overdose of extended-release preparations. At the end of 12 hours, the estimated concentrations of NAC in plasma in SNAP and double dose of Australian are twice those with the traditional and Australian regimens. In contrast, the SNAP and Australian 2-bag regimens have the lowest NAC plasma concentration at the end 20 hours. Nevertheless, the plasma NAC with the SNAP regimen is still detectable up to 8 hours after infusion cessation.

For comparison, **Figure** 2-6 displays overlayed simulated NAC concentrations regimens of SNAP regimen compared to the standard and the Australian protocol.

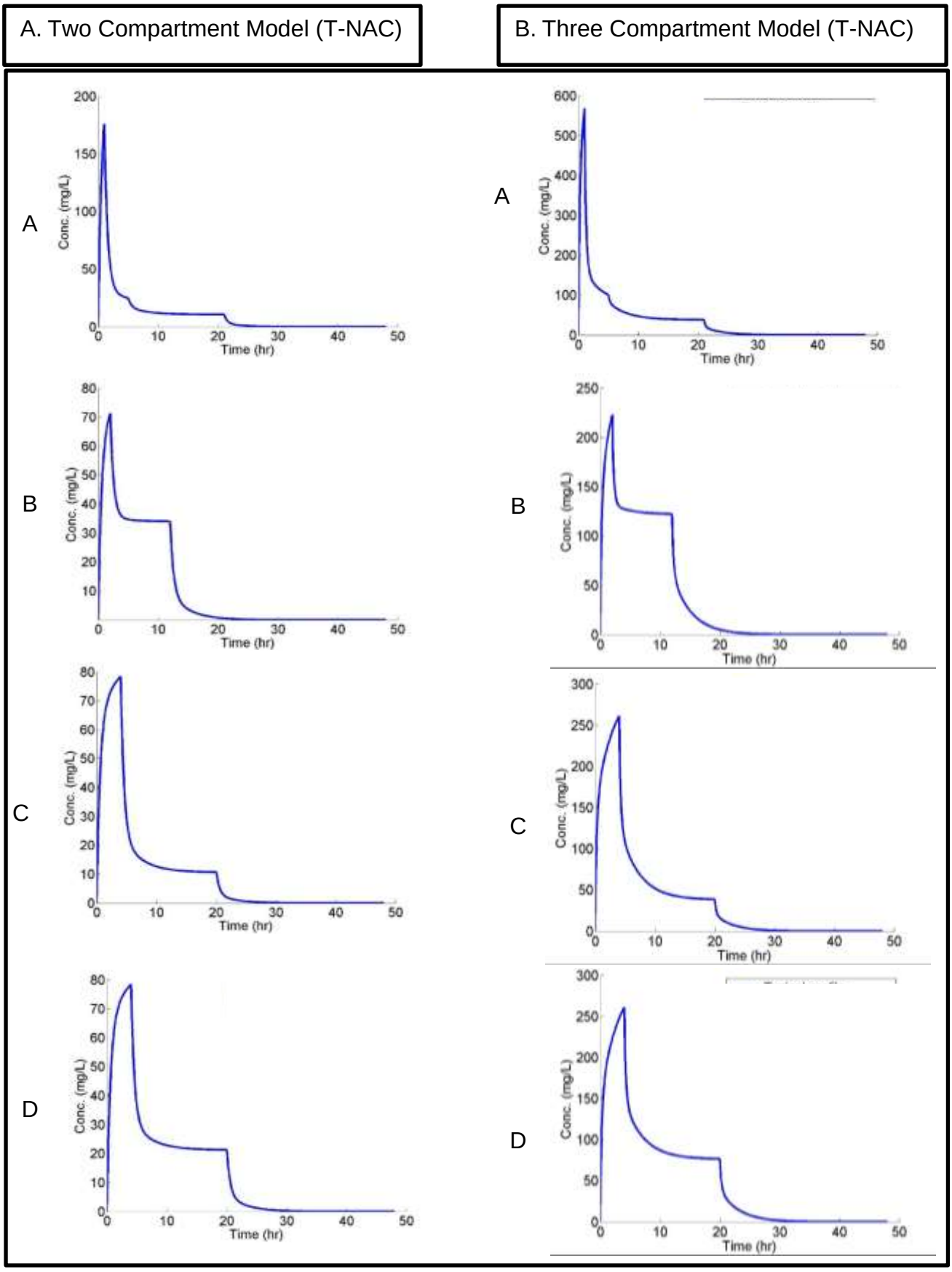


Figure **2-3: Total NAC (T-NAC) concentration-time modelling based on two compartment and three compartment model. A. Conventional regimen. B. SNAP regimen. C. Australian regimen. D. Double dose Australian regimen.**

C. Three Compartment Model (R-NAC)

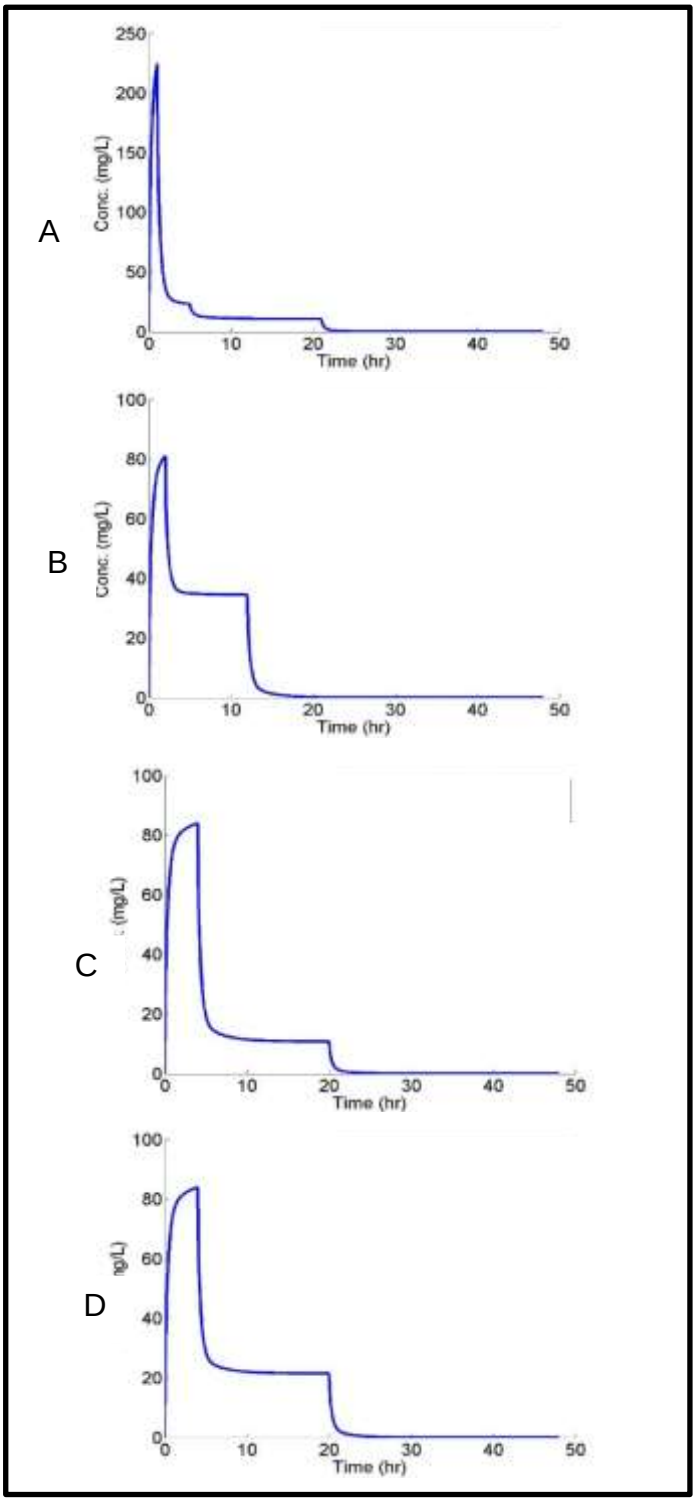


Figure 2-4: Reduced NAC (R-NAC) concentration-time profile modelling based on three compartment model. A. Conventional regimen. B. SNAP regimen. C. Australian regimen. D. Double dose Australian regimen.

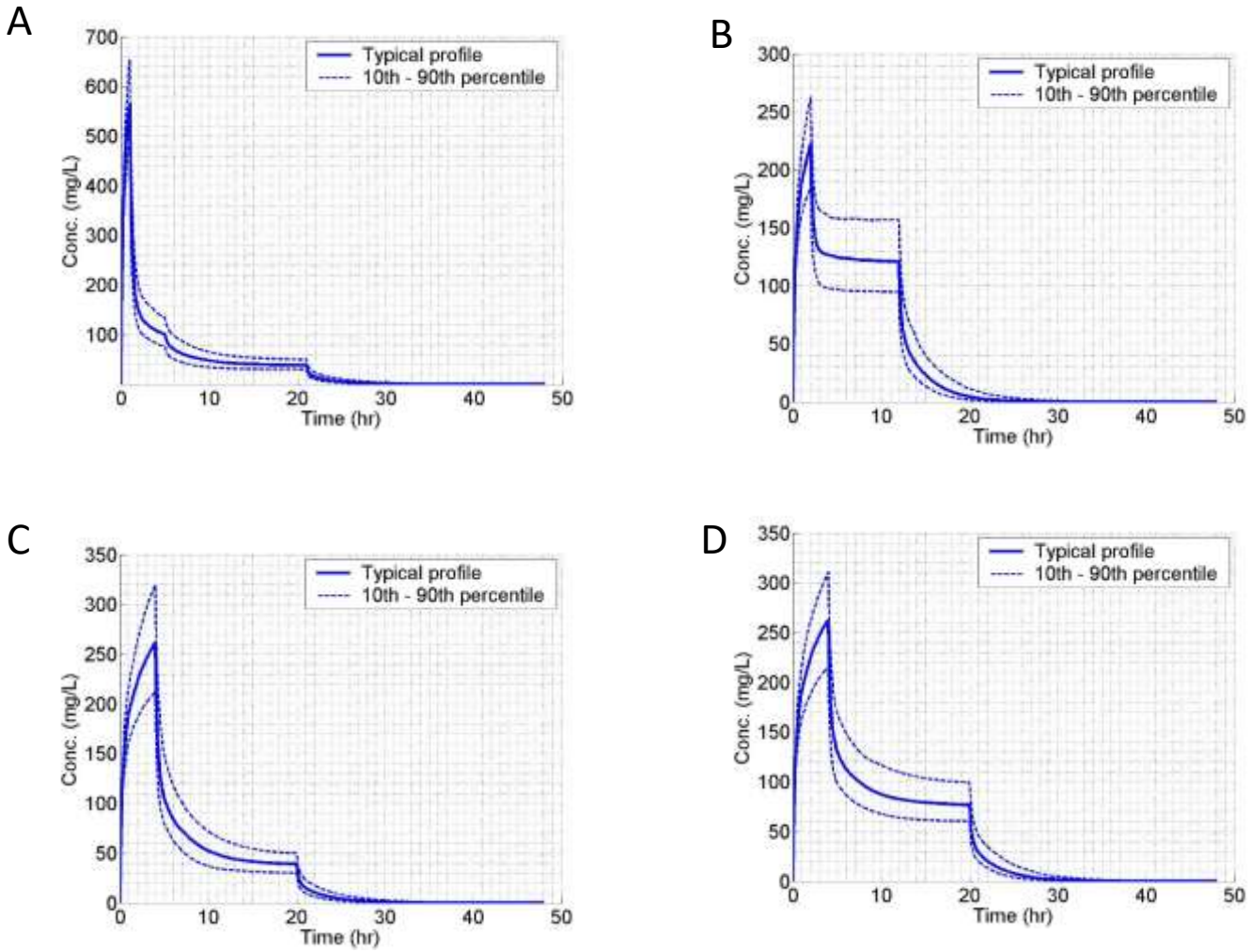


Figure 2-5: Total (T-NAC) regimen concentration-time profile with 90th and 10th percentiles based on three compartment model. A. Conventional regimen. B. SNAP regimen. C. Australian regimen. D. Double dose Australian regimen.

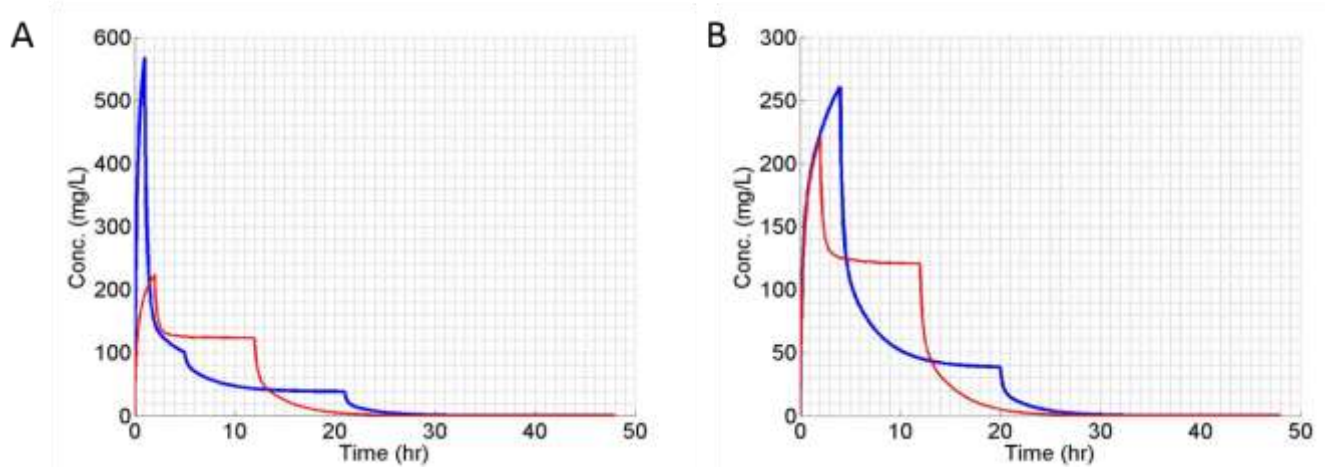
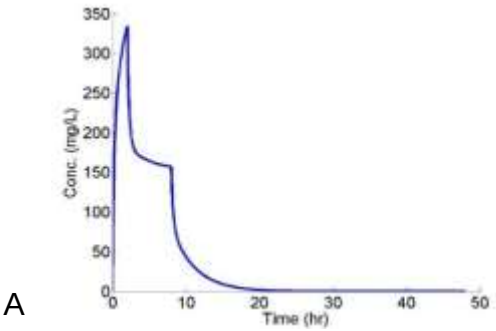


Figure 2-6**:overlay simulated PK profile of A. SNAP regimen with standard regimen. B. SNAP regimen with Australian regimen.**

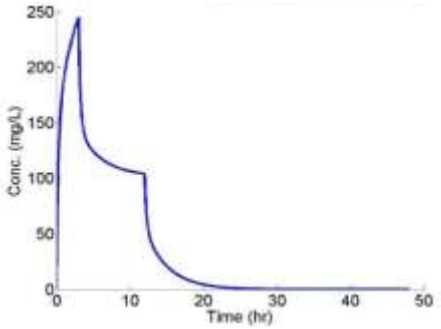
Simulations of the NAC concentration-time profile were performed for 8 different regimens using alterations of the loading and maintenance dose and total durations of infusion (**Figure 2-7**). Slowing the rate of infusion of the loading dose reduced the peak concentration although this is higher when a larger loading dose is given, for example, initial infusion of regimen (D) and regimen (H) have the same rate, which is 50 mg/kg/h; however, the regimen (D) has higher peak concentration and the time to maximum concentration is slower compared to the regimen (H). Hence, the rate of loading dose is the same in the SNAP and Australian regimen, which is 50 mg/kg/h, however the Australian regimen in the **Figure 2-5** shows higher peak concentration compared to the SNAP as a result of the larger loading dose in Australian regimen (and administered over a longer period) than for SNAP.

There are differences in the steady state concentrations achieved with the different regimens even when they have the same rate of second infusion. For example, the flat concentration of regimen (A) and (H), regimen (B) and (D), and regimen (G) and (F) are around 160 mg/l with infusion rate 25 mg/kg/h, 105 mg/l with infusion rate 16 mg/kg/h, and 185 mg/l with infusion rate 31 mg/kg/h, respectively. The conventional regimen and Australian regimens demonstrate similar lower steady state concentration after second dose with rate 6.25 mg/kg/h compared to steady state concentration of the SNAP regimen 120mg/l with infusion rate of maintenance dose 20 mg/kg/h.



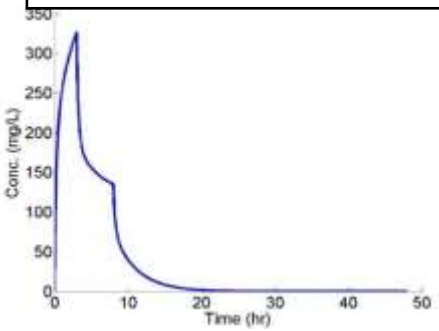
A

150 mg/kg over 2h, 150mg/kg over 6h



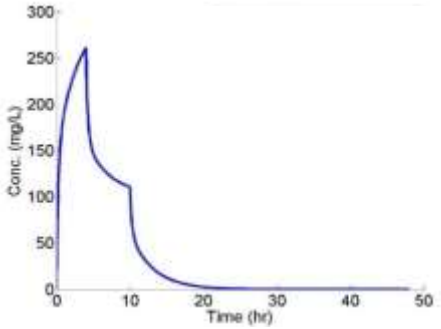
B

150 mg/kg over 3h, 150mg/kg over 9h



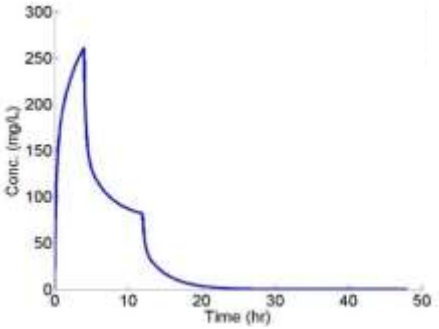
C

200 mg/kg over 3h, 100mg/kg over 5h



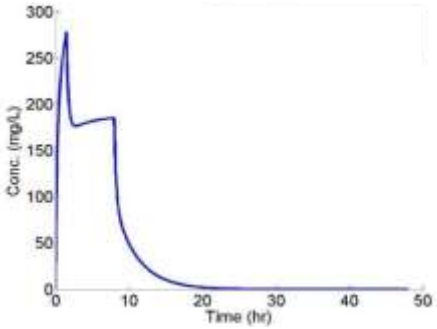
D

200 mg/kg over 4h, 100mg/kg over 6h



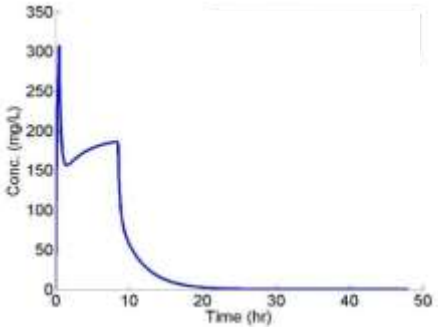
E

200 mg/kg over 4h, 100mg/kg over 8h



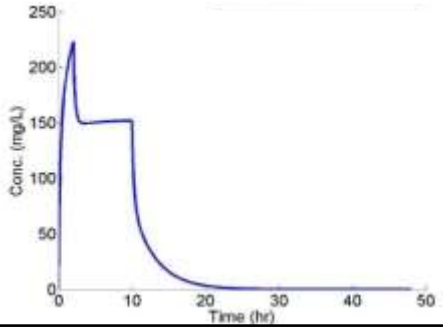
F

100 over 90 minutes and 200 over 6.5h



G

50 mg/kg over 30minutes and 250 mg/kg over 8h



H

100 mg/kg over 2 h, 200 mg/kg over 8h

Figure 2-7 Different NAC regimen simulated based on total NAC pharmacokinetics parameters and three compartment model.

Figure 2-8 shows the simulation of total and reduced NAC for the SNAP regimen based on a three-compartment model with different lag times between the 1st and 2nd infusion, reflecting potential delays in starting the 2nd infusion in clinical practice. This shows that total NAC concentration declines to below 30 mg/l when the second infusion is delayed by up to 4 hours, but the concentration increases rapidly backs to approximately 120 mg/l after resumption of the infusion. The concentration of reduced form drops to 10 mg/l, and negligible concentration when the lag time between first and second dose are 1h, and 4 h, respectively. As total NAC concentrations with the SNAP regimen remain higher during the maintenance dose compared to the other regimens, even delays of up to 4h in starting the second infusion may not have a large effect on steady state concentration.

As some patients will require additional NAC treatment at the end of 12 hours, we simulated concentrations with an extended SNAP regimen with different intervals between 2nd bag and the extended third infusion **(Figure 2-9**). The plasma concentration falls sharply from the steady state concentration of 120 mg/l to 30 and 20 mg/l respectively after a 1h and 2h interval before the third bag is commenced. After 3- 4 hours interval, the concentrations decrease to 10 mg/l. Even though stopping the infusion causes NAC plasma concentration to fall by more than third compared to the steady state concentration, NAC plasma concentration returns rapidly to steady state once the extended dose has begun.

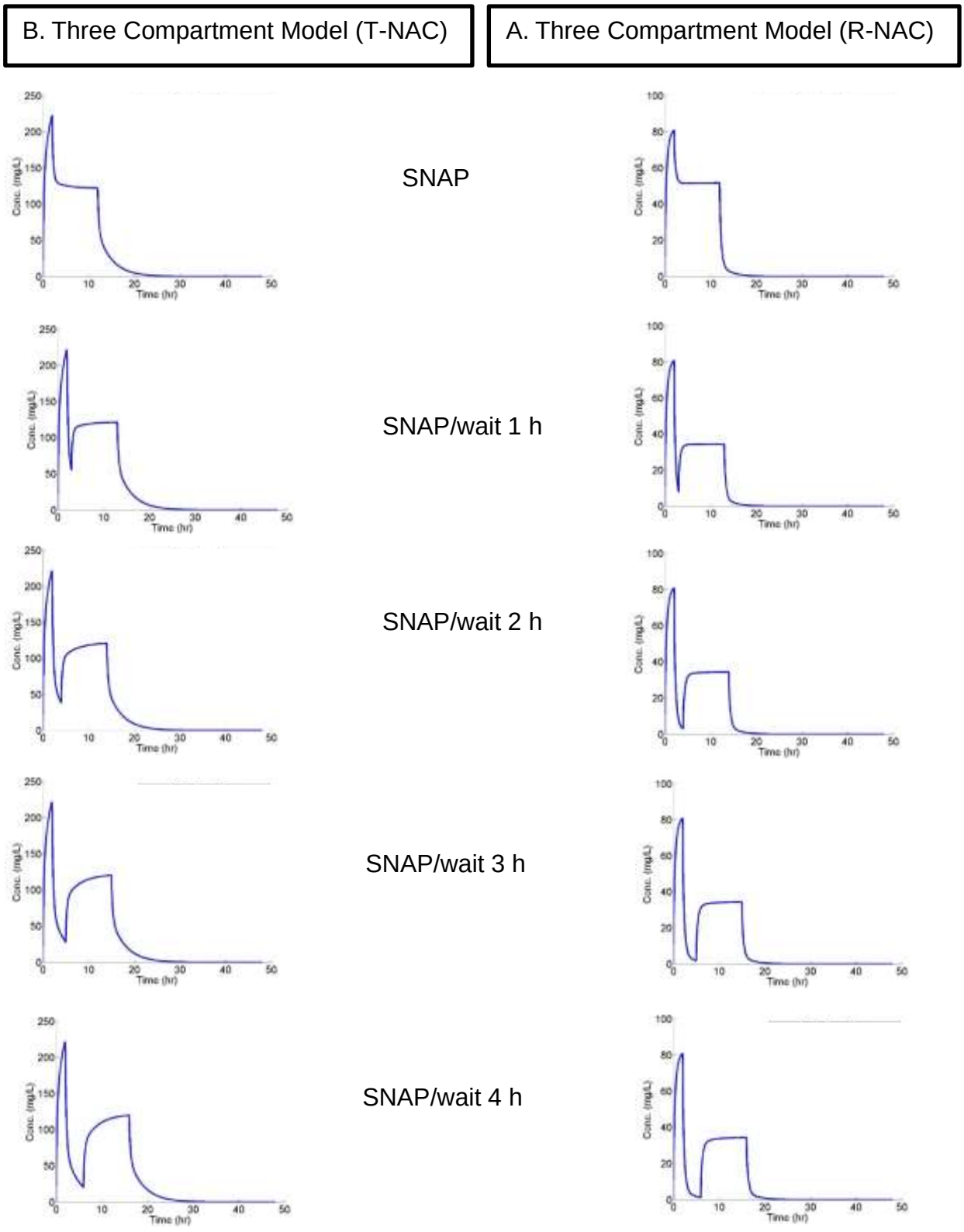


Figure 2-8 SNAP regimen simulated based on total NAC (T-NAC) and reduced NAC (R-NAC) when there is lag time between loading dose and maintenance dose.

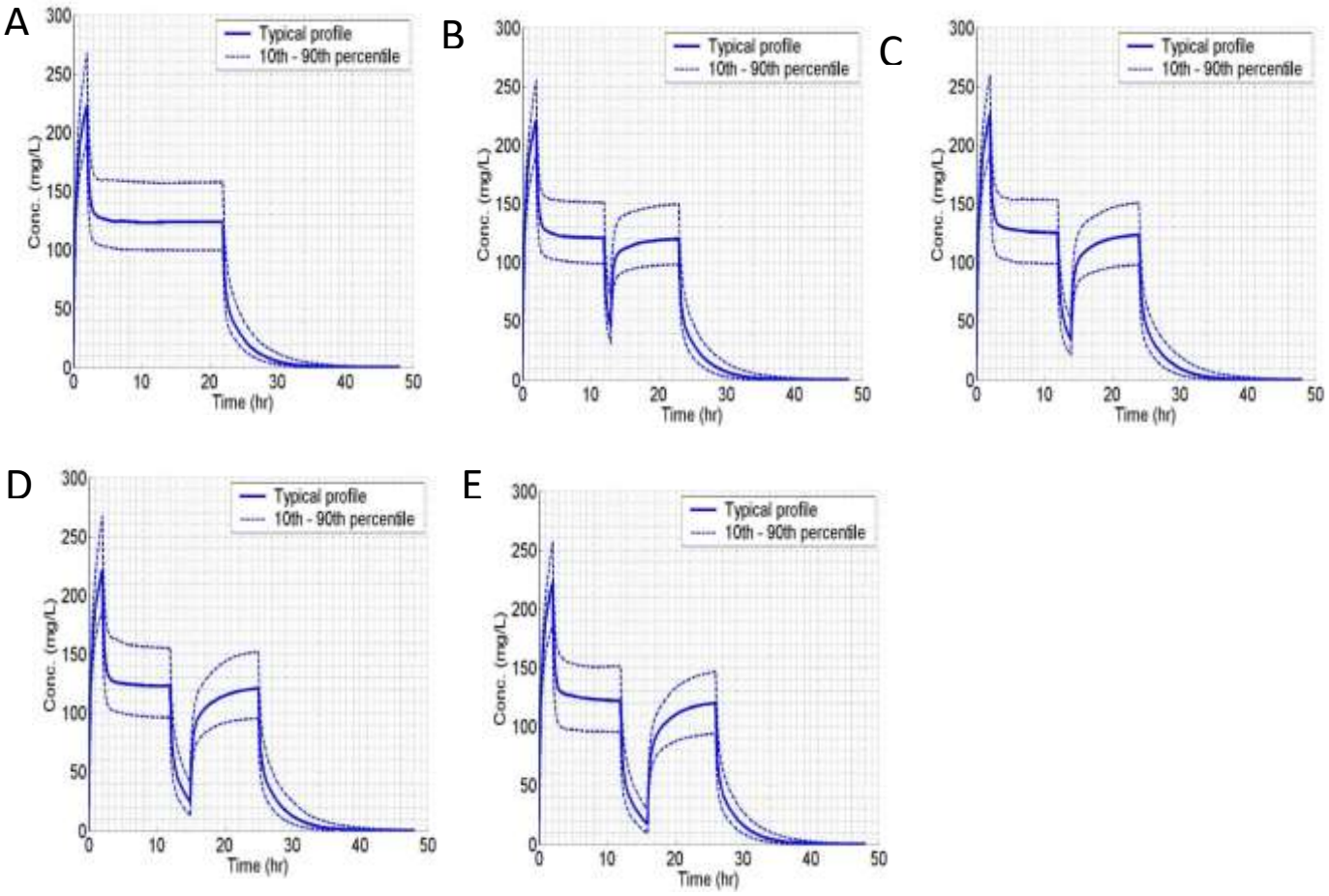


Figure 2-9 Extended 12 hours regimen of SNAP protocol with third bag 100mg/kg over 10 hours. A. No gap between the second dose and third one. B.one hour gap. C.2 hours gap. D. three hours gap. E. four hours gap.

2.4. Discussion

The current 3-bag 21 h NAC regimen for treatment of paracetamol overdose is associated with high risk of NAARs as half of the total dose is given within one hour at a high infusion rate of 150 mg/kg/h. There has been a lot of interest in modifying this regimen using a 2-bag regimen aiming to slow the infusion rate of the loading dose and simplify the regimen (84, 126).

The SNAP regimen was initially derived based on a one compartment pharmacokinetic model(122) and was shown in a clinical trial to significantly reduce the proportion of patients requiring antihistamine treatment to treat NAC infusion-related NAARs (96). However, the study was not powered for efficacy and the

study protocol did not evaluate management steps at the end of the 12 h infusion to allow SNAP implementation into routine clinical practice. Therefore, we simulated the most recent published modified NAC regimens including SNAP to predict the NAC concentration-time profile to provide justification for an optimal SNAP protocol for use in clinical practice.

The simulations showed that the reduced plasma NAC concentrations are lower compared to the total NAC in all regimens as a result of higher apparent volume distribution in reduced form than total NAC (0.064 vs 0.037 l/kg). The slower clearance of total NAC results in detectable plasma NAC 8 hours after stopping the infusion, whereas reduced NAC became undetectable within 2 to 3 hours of infusion cessation. Total NAC concentration has been used in most pharmacokinetic studies of intravenous acetylcysteine. We performed simulations of total NAC with a 3-compartment model to estimate plasma NAC concentration for optimisation of the NAC regimen.

The simulated concentrations with the SNAP regimen showed lower peak and higher steady state NAC concentrations than other regimens, which may theoretically be superior in causing less initial infusion reaction and in maintaining enough glutathione synthesis in the liver. The minimum NAC plasma concentration required for effectiveness or developing infusion related side effect is not known(127). A novel dosing regimen of loading dose 110 mg/kg over 5h or 200 mg/kg over 9 h had been simulated with lower infusion rate to investigate the effectiveness of minimum NAC concentration required for prevention of hepatocellular damage post paracetamol overdose. The study found that the novel regimen using a loading dose of around 23 mg/kg/h instead of 150 mg/kg/h in conventional regimen provided area under the curve (AUC) similar or higher than AUC of conventional regimen in 90% of the simulations(109). The study authors suggested that the novel regimen delivered the same amount of NAC as the conventional regimen while expected to have less NAC adverse reaction and similar effectiveness. Based on this assumption, SNAP regimen, unlike the conventional regimen and Australian regimen, can maintain the maintenance dose at 20 mg/kg/h, which may be important in patients with large overdoses or taken extended-release preparations when the paracetamol concentration may be elevated for longer.

The estimated NAC infusion rate of 6.25 mg/kg/h has been estimated to be sufficient as long as paracetamol half-life is 4 hour or less, liver size is 1.5 L, and paracetamol body burden 16 g or less(128). However, after massive overdose or in patients whose paracetamol concentration at 4h post overdose exceeds 300 mg/L, the 6.25 mg/kg/h infusion rate may not be sufficient (79, 129). Theoretical calculations by Rumack and Bateman(79) suggest that the maintenance infusion rates when the 4-hour extrapolated paracetamol concentration exceed 150, 300, 450, 600 mg/L should be 6.25, 12.5, 18.75, and 25 mg/kg/h, respectively. Even when NAC is initiated within 8 h of acute ingestion, the proportion of patients developing hepatotoxicity increase up to 30% when patients taking large paracetamol overdoses are treated with 6.25 mg/kg/h of intravenous NAC as maintenance infusion.(130-132). Therefore, those patients may require an intensified dose of NAC, which the SNAP regimen provides as a 20 mg/kg/h infusion rate which would be expected to be an adequate dose for the vast majority of patients with paracetamol overdose.

The next issue is the safety of shortening the duration of the NAC regimen from 21 h to 12 h. This would reduce costs and the length of hospital stay and this would be advantageous as long as the safety and efficacy are comparable to the 21h standard protocol (93, 122). Tailoring the duration of intravenous NAC therapy according to the laboratory criteria at the end of 12 h would give a further advantage to the SNAP regimen in those patients with paracetamol overdose (96). However, the conventional intravenous regimen was developed based on five 4-hour half-lives of therapeutic dose of paracetamol(74, 133) and there may be a concern that the shortened duration of NAC regimen might be associated with higher incidence of hepatotoxicity especially in high risk groups(134). However, the serum paracetamol concentration was undetectable and liver enzymes were not elevated at the end of first 12h treatment of conventional regimen assuming that elimination half-life is less than 3.6h and 90% of paracetamol was excreted with 12 h particularly in low risk group of patients(135). Shortening the duration of NAC treatment has also been reported with the 72h oral NAC protocol, based on the assumption of 12 h half-life after paracetamol overdose. Studies confirmed that shortening oral NAC regimen to 20h oral NAC is safe and effective compared to the original 72h oral NAC protocol. when paracetamol concentration, at the end of

20h oral NAC regimen, is undetectable, ALT and INR were normal or unchanged, and clinical manifestations are improved (136, 137). Bateman et al(96) reported in the SNAP clinical study that the incidence of hepatotoxicity at the end of the 12h regimen was similar to the 21h conventional regimen, although this study was not powered for efficacy.

An extended duration of NAC therapy is indicated clinically at the end of the conventional 21h NAC protocol(26) in patients who have evidence of developing liver injury on blood tests at the end of the infusion. There are no published studies of NAC plasma concentrations achieved with extended infusions of NAC. Simulations of the Australian 2-bag protocol – 250 mg/kg over 12 h; 200 mg/kg over 4 h then 50 mg/kg over 8 h, showed that NAC can be detectable in plasma up to 8 h after infusion cessation, which might suggest some continuing hepatoprotective effect for some time after discontinuation of treatment (126). Our simulation of the NAC concentration-time profile for the extended SNAP regimen shows that it maintains a constant steady-state concentration of 120 mg/l. Even with a delay of up to 4h in starting the third infusion, the NAC plasma concentration is not expected to drop below 10 mg/l, which is comparable to the conventional regimen steady state concentration of 12.5 mg/l. Therefore, the extended SNAP regimen provides a higher total dose of NAC of 500 mg/kg over 22h compared to 300 mg/kg with the 21h conventional regimen, a lower peak NAC concentration and a higher steady-state NAC concentration. This may translate into fewer adverse reactions overall and potentially increased efficacy for those presenting with large paracetamol overdoses.

2.5. Conclusion:

Our pharmacokinetic simulations of total plasma NAC based on a three-compartment model show that the simple SNAP regimen predicted lower peak NAC concentrations and higher steady-state concentrations than the conventional 21h regimen and also allowed for the 12h regimen to be extended, providing a higher total NAC dose and sustained NAC concentrations over 22h. This provides justification for evaluating this approach in clinical practice to confirm whether it causes fewer NAC adverse effects but maintains comparable efficacy.

CHAPTER 3

CLINICAL EVALUATION OF A SHORTER 12 H ACETYLCYSTEINE REGIMEN

Chapter 3 Evaluation of a shorter 12 h acetylcysteine regimen for the treatment of paracetamol overdose

3.1. Introduction

Paracetamol overdose is common in developed countries, accounting for 32.8% of all overdose cases in emergency departments. Of these, 68.8% have required hospital admission for treatment with intravenous NAC (138). Although NAC is highly effective in preventing paracetamol hepatotoxicity and death when administered soon after overdose, 2-5% of patients can suffer acute liver failure (139). The annual average deaths from drug poisoning by paracetamol in England and Wales is 200, although the number had steadily decreased over last 20 years (140).

3.1.1. Risk stratification

NAC is the optimal treatment for paracetamol overdose, although its effectiveness is dependent on the pattern of paracetamol overdose (acute or staggered)(141), time from overdose ingestion to NAC initiation(142), paracetamol plasma concentration and overdose size(130). NAC treatment is not required for all paracetamol overdoses but indicated only for patients at risk of developing hepatotoxicity(143) based on a paracetamol treatment nomogram. The Rumack-Matthew nomogram used a treatment line starting at 150 mg/l at 4 hours. The original treatment nomogram used in the UK consisted of a line starting at 200 mg/l at 4 hours post-ingestion and falling exponentially with a half-life of 4 hours. In patients with risk factors increasing their susceptibility to liver injury (144) (see **Table 3-1**), a lower treatment line starting at 100 mg/l at 4 hours was used.

Table 3-1: Risk factors for paracetamol-induced liver injury(144)

1	Protein calorie malnutrition.
2	Chronic excessive alcohol consumption
3	Concomitant ingestion of drugs inducing hepatic enzyme activity; for example, St John's wort, carbamazepine, phenytoin, and rifampicin

In the UK, the Commission for Human Medicines recommended in 2012 that a single treatment line starting at 100 mg/l at 4 hours be used (the 100-line). In North America and Australia, the 150-line is still used. This is important when attempting to compare the efficacy of NAC regimens in different countries.

The 100-line is very conservative, regardless of the presence of risk factors, but was recommended in the UK due to the paucity of evidence supporting the validity of these risk factors and difficulty in assessing accurately whether they are present or absent in patients presenting with a paracetamol overdose. The risk of liver injury is very low in patients taking an overdose of 12 g or less with a low paracetamol concentration and normal values for INR and ALT at presentation.(145).

Delay in initiating NAC treatment beyond 8 or 10 h of overdose(121), staggered ingestion, 4 h extrapolated paracetamol concentration above 300-line(130), or massive overdose greater than 32 g are predictors of hepatotoxicity development.

3.1.2. UK NAC treatment guideline

The decision to initiate or continue NAC treatment in patients taking a single acute overdose within 24 h is based on whether the paracetamol concentration is above the treatment line. The decision to initiate NAC is also based on the time of overdose ingestion and dose pattern. Current UK recommendations are to start NAC immediately if the time of ingestion is more than 8 hours after overdose, or the time of overdose is unknown or if the overdose is staggered. If the time of ingestion is less than 8 hours, NAC should only be started when the paracetamol concentration taken at least 4 h after overdose is above the treatment line. In patients who present more than 24 h after ingestion or with repeated supratherapeutic paracetamol ingestions, treatment is recommended if the paracetamol concentration is above 10 mg/L, ALT >40 IU/l, or jaundice or liver failure are present on examination **(Figure 3-1**)(26).

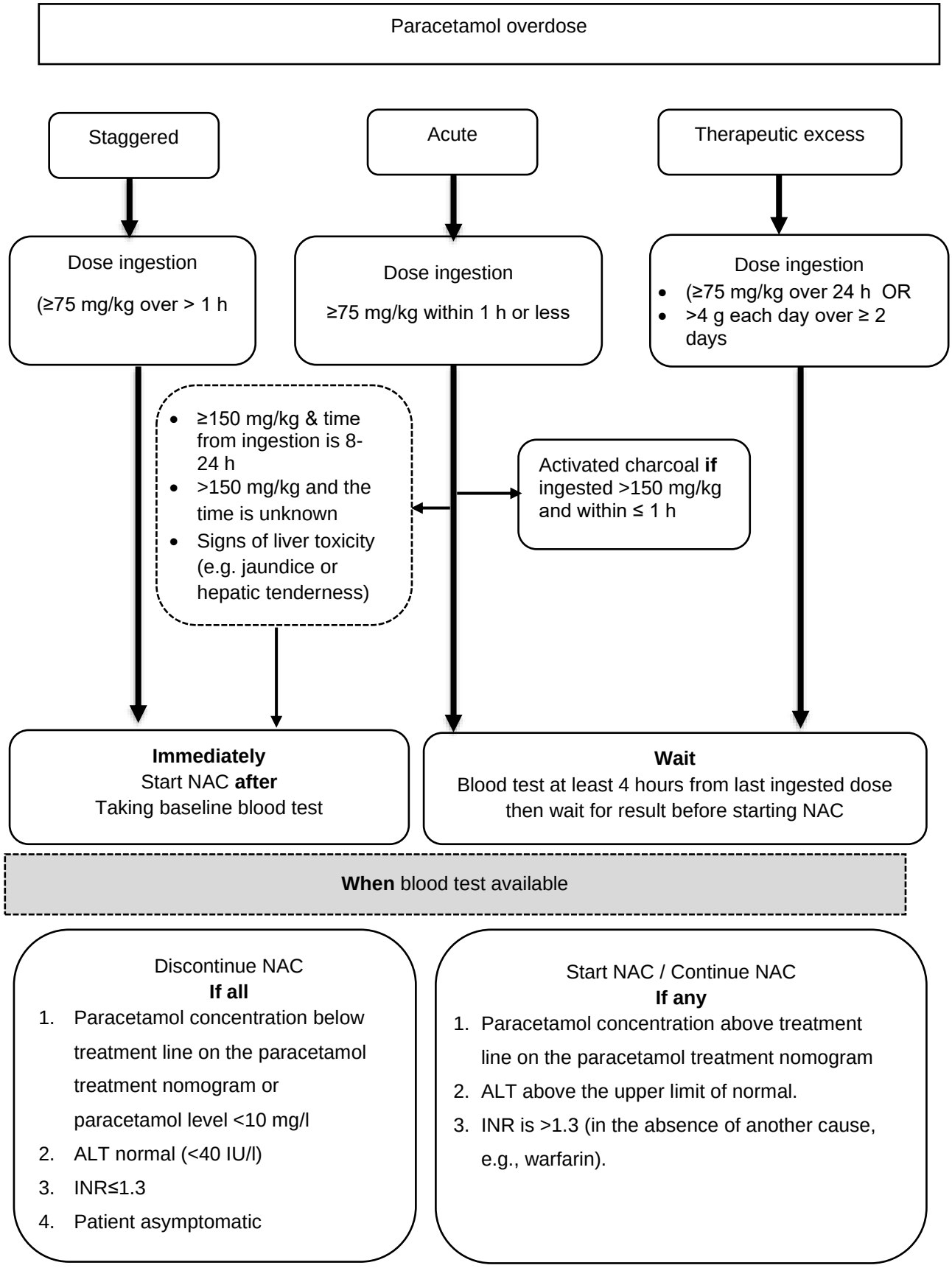


Figure 3-1: Criteria for NAC treatment in paracetamol overdose

3.1.3. Predictors of hepatotoxicity

Even though the paracetamol concentration plotted on the treatment nomogram has been used for decades to identify those who need NAC treatment, the nomogram is not a good predictor to identify those patients who are at low or high risk of developing hepatotoxicity despite NAC treatment.

Intravenous NAC is associated with infusion NAARs, mostly occurring shortly after starting the infusion when NAC concentrations are at their highest. These reactions may lead to the infusion being temporarily discontinued and consequently treatment delay. The severity of adverse reaction is variable, nausea and vomiting may require treatment with antiemetic or urticarial rash might need antihistamine treatment. More severe NAARs may include hypotension, angioedema and bronchospasm and these require stopping the infusion and treatment with fluids and/or bronchodilators. The infusion can be restarted at a slower rate once the reaction subsides(146). It has been shown that paracetamol has a protective effect against infusion-related adverse reactions; patients who have low paracetamol concentration, whether due to low overdose ingestion or late presentation, are at higher risk of developing adverse reactions(147). Hence, low paracetamol concentrations and high concentrations of NAC increase the risk of NAARs during NAC therapy.

The most widely used intravenous NAC regimen is 3-bag, 20.25 h regimen, which has been used over 4 decades. Several studies have showed that NAARs occur in 8.2% of patients treated with the standard NAC regimen (148-150) and is linked with the high initial rate of infusion. Extending the loading dose from 15 minutes to 1 h to reduce the initial NAC concentration reduced the rate of adverse reactions although this was not statistically significant(82). Nevertheless, the 3-bag 21 h regimen has now superseded the initial Prescott regimen in clinical practice. A further disadvantage of the 3-bag infusion is its complexity, which may be associated with prescribing and administration errors.

3.1.4. SNAP regimen

The SNAP regimen is an alternative regimen, first proposed in 2013 to reduce the risk of infusion side effects and NAARs, and to simplify the original regimen. It was designed using using pharmacokinetic simulation (122). Other alternative regimens have since also been proposed and evaluated by comparison to the standard regimen in recent years. Most studies show that increasing the loading dose infusion to 2 hours or more significantly diminished the occurrence of NAC infusion side effect (86, 91, 134, 151).

A randomised double blind study showed that the SNAP 12 h regimen (first dose: 200 mg/kg over 2 hours, second dose: 100 g over 10 h) was significantly better compared to the three-bag standard NAC regimen in number of reported severe NAARs (5% vs 28%, P=0.001) and number needing rescue antiemetic treatment (39% vs 65% , P=0.001), respectively(96). A number of observational studies show that the Australian two-bag regimen (loading dose: 200 mg/kg over 4 hours and maintenance dose: 100 mg/kg over 16 h) causes significantly fewer NAARs and need for antihistamine therapy during NAC infusion. Even though these studies are not powered to demonstrate efficacy, there is growing evidence that the two-bag regimens appear to provide similar benefit to the 21 h 3-bag regimen in terms of preventing the development of hepatotoxicity. However, it has been argued that these studies are insufficiently powered for efficacy and the majority of patients included were at low risk of hepatotoxicity. In order to allow a change in clinical practice to the SNAP regimen, larger studies are required that include patients at higher risk such as late presenters and those with large overdoses. There is also uncertainty as to whether a large initial dose of NAC is required after a massive paracetamol overdose(152). In June 2021, the SNAP regimen was added on TOXBASE as an alternative NAC regimen for patients with previous severe NAARs to NAC, but the SNAP regimen is not licensed by the Medicines and Healthcare products Regulatory Agency (MHRA).

The SNAP regimen has three obvious advantages which are simplicity, fewer infusion side effects and shorter duration of treatment. Using the pharmacokinetic simulation described in chapter 2, we designed a SNAP protocol for implementation in clinical practice with the objective of evaluating its effectiveness in preventing hepatotoxicity in patients with paracetamol overdose.

3.2. Clinical study

3.2.1. Aim

The main study objective was to compare the efficacy of a 2-bag 12 h acetylcysteine (NAC) regimen ('SNAP') with the current 3-bag 21 h NAC regimen in patients with acute paracetamol poisoning.

3.2.2. Study design and setting

The study was designed as a bidirectional cohort study comparing a retrospective cohort of patients treated with the standard 21 h regimen with a prospective cohort of patients treated with the SNAP protocol following paracetamol overdose in three different hospitals in the UK (Royal Victoria Infirmary in Newcastle upon Tyne (RVI), St Thomas Hospital London (STH), and Royal Infirmary in Edinburgh (RIE)).

In this ongoing cohort study, all patients treated with NAC in these hospitals were included from the time of starting NAC infusion to discharge.

SNAP regimen:

Prospective cohort (1st October 2016 to 30th September 2020): at RVI.

Prospective cohort (1st June 2016 to 31st December 2019): at STH.

Prospective cohort (September 2015 to September 2017): at RIE.

Standard regimen:

Retrospective cohort (September 2012 to September 2016): at RVI, STH, and RIE

3.2.3. Patient selection

All patients with paracetamol overdose were assessed and treated with NAC according to the TOXBASE revised guidance in 2012 (toxbase.org) (see Figure 3-2)

Inclusion criteria:

- Age 16 years or older.
- Patients presenting with a single acute overdose, staggered overdose, or therapeutic excess of paracetamol and requiring NAC treatment as per UK guidelines. (Paracetamol concentration-time graph is 100 mg/l at 4 hour or above for acute single overdose).

Exclusion criteria

- Patients less than 16 years old.

3.2.4. Study protocol

All patients who presented with an overdose of paracetamol were assessed and information about timing and dose of paracetamol ingested, patient history whether overdose was intentional or accidental was elicited.

Patients eligible for NAC treatment were treated with the SNAP regimen:

Loading infusion: 100 mg/kg NAC in 200 mL 5% dextrose over 2 hours (100 mL/hour) followed by:

Maintenance infusion: 200 mg/kg NAC in 1000 ml 5% dextrose over next 10 hours (100 ml/h)

Patients requiring treatment with NAC were admitted to the medical admission unit until discharge. A pre-defined and written SNAP protocol was used to enable decision about discharge or continuation of NAC treatment. All patients had blood tests taken at the end of the 12 h infusion. Patients who were at least 24 h post-ingestion were deemed to require additional NAC treatment if: ALT>2xULN; ALT doubled or more from admission; paracetamol>10; ALT> ULN and INR>1.3. Patients who were less than 24 h post-ingestion required additional treatment if: ALT>2xULN; ALT doubled or more from admission; paracetamol>20; ALT> ULN and INR>1.3. Those who did not require additional treatment had an additional blood sample taken at least 24 h post overdose to ensure that they meet the criteria for discharge. There were two differences between the three hospitals in the study procedure. First, in RIE, unlike RVI and STH, blood samples were taken two hours before the end of 12 h SNAP regimen instead at the end or just before the end of the 12 h NAC regimen. Second, the upper limit of normal of ALT in RVI and STH was 40 IU/l, but in RIE it was 50 IU/l.

Figure 3-2 shows the clinical protocol for treatment with the SNAP regimen during study period. This protocol was peer-reviewed and approved by the Clinical Standards Group of the National Poisons Information Service for use in hospitals with clinical toxicology expertise in July 2015.

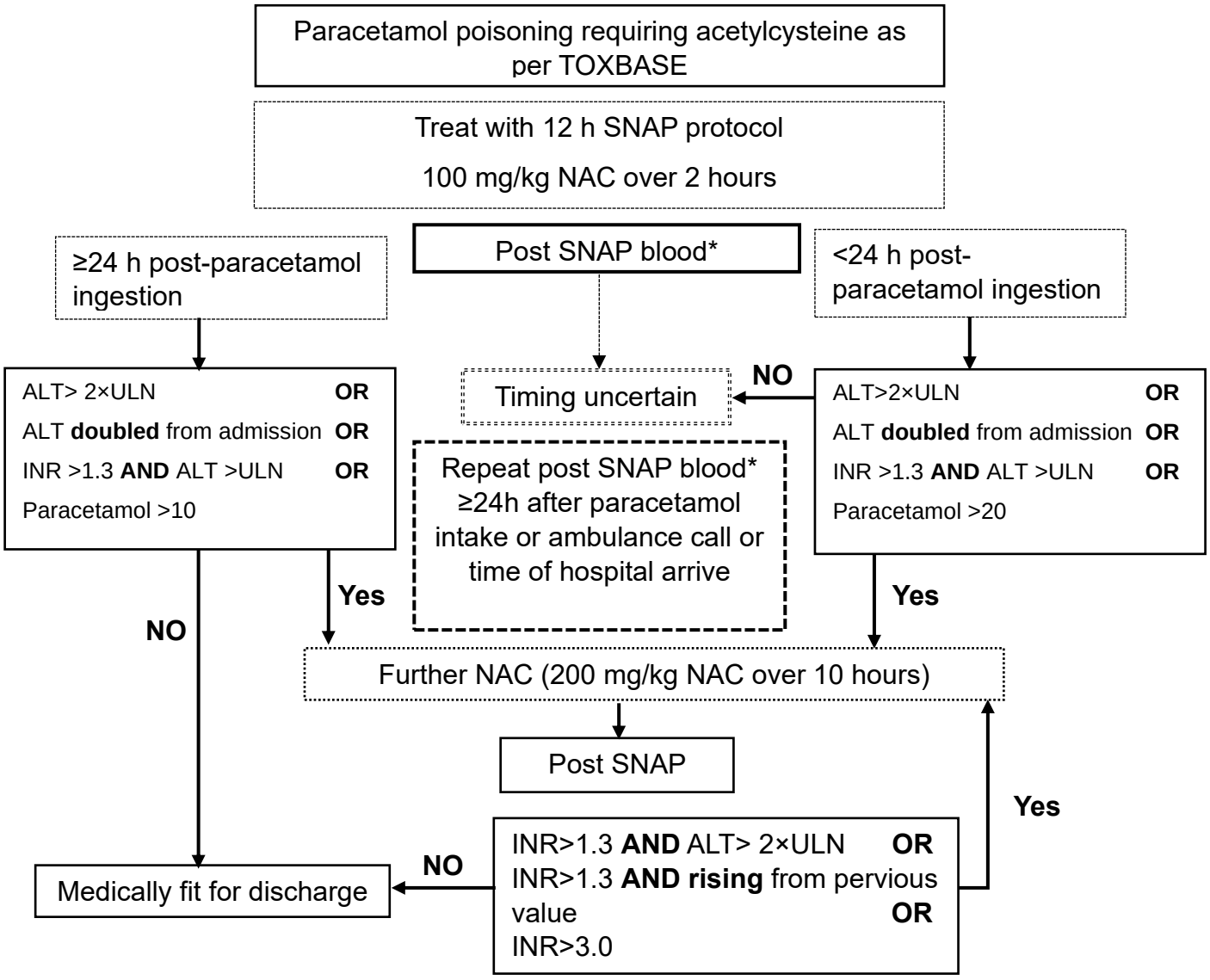


Figure 3-2: A clinical protocol for management of patients treated with the SNAP regimen

Between September 2012 when the UK Commission on Human Medicines (CHM) made recommendations on the management of paracetamol overdose until the SNAP implementation period, the NAC regimen used was the 21 h 3-bag regimen. Patients could be discharged after treatment if ALT was less than 80 IU/l, ALT not doubled or more than doubled from admission, INR<1.3, and Paracetamol <20. If patients did not meet these criteria, NAC infusion would be continued by repeating the third bag of the standard protocol.

3.2.5. Approvals

Local approvals were sought from the Medicines Management Committee in each of the three hospitals for routine implementation of the SNAP protocol as standard care. Patient consent was not required. Data collection was part of routine standard care and anonymised data was collected as a prospective audit of the SNAP protocol implementation in each of the 3 hospitals. The audit was conducted in accordance with the Data Protection Act 1998.

3.2.6. Data collection and processing

SNAP

In the 3 hospitals where the SNAP regimen was implemented, data was collected prospectively as an audit for all patients admitted with paracetamol overdose and required NAC treatment in that period. Patients received routine clinical care as part of a specialist clinical toxicology service. All patient data formed part of the routine electronic medical record in the hospital. As part of the prospective audit, clinical data were retrieved from the electronic medical record and entered in a pre-formatted excel sheet. Raw data collected in RIE from the period September 2015 and 2017 and included in the publication by Pettie et al 2019 was kindly provided by Prof Dear for inclusion in this data analysis which included additional data from St Thomas Hospital and Royal Victoria Infirmary from 2017 onwards.

Standard regimen

Similar data using the electronic medical record of patients treated in these 3 hospitals with the 21 h regimen between September 2012 to the beginning of the SNAP implementation in each hospital were collected as retrospective audit. Clinical data with the standard 21 h regimen was collected using a pre-formatted Excel sheet.

3.2.7. Outcome measures

Primary outcome:

- Proportion of patients developing Peak ALT >1000.

Secondary outcomes:

- Proportion of patients developing peak INR>2.
- Proportion of patients developing acute liver injury (ALT>100).
- Proportion of patients with NAARs diagnosis and received medication of antihistamine and/or corticosteroid.

In each patient, ALT and INR were measured at least twice, at baseline before NAC started and at the end of second infusion. In some patients, additional blood samples were taken either as a 24 h post-ingestion blood sample or after additional treatment NAC.

3.2.8. Statistical analysis

Demographic details of patients included in the analysis were described using simple descriptive statistics. Dichotomous data are represented as absolute numbers and percentages. Differences between proportions were described as the absolute difference with the 95% confidence intervals. Hypothesis testing was undertaken using chi-squared tests, Fisher's exact test, or the equivalent non-parametric test, as appropriate. Continuous variables that were not normally distributed (as per the Kolmogorov Smirnov normality test) are presented as medians (interquartile range) and were compared using the Mann–Whitney U-test. A P-value of <0.05 was considered as statistically significant. All statistical analyses were performed using IBM SPSS version 27. Analyses for the outcomes of peak ALT>1000, ALT>100 and INR>2 included data published in 2019 but with additional data from Newcastle and London from 2017.Analysis for anaphylactoid reactions was performed for the Newcastle and London cohorts only.

Binary logistic regression was performed to determine which factors were associated with development of hepatotoxicity. Covariates considered for entry into the model included time from ingestion to acetylcysteine treatment, age, sex, weight, ingested paracetamol dose, NAC regimen used (SNAP or standard) and paracetamol-aminotransferase multiplication product. Univariate regression analysis was performed to identify variables significantly associated ($p<0.05$) with hepatotoxicity to include in the multivariate regression analysis. Models were compared using the likelihood ratio test, and Hosmer-Lemeshow goodness of fit test. Results are presented as unadjusted and adjusted odds ratios (OR) with 95% confidence intervals.

3.3. Results

In total, 4818 patients were treated with NAC. There were 77 patients who had hepatotoxicity (ALT>1000) on admission who were excluded from the analysis. There were 2946 patients treated with the SNAP regimen and 1795 patients treated using the standard 21 h regimen.

The breakdown of patients according to the pattern of overdose for each regimen (SNAP and standard) is shown in

Figure 3-3 with the proportion of patients with the primary outcome (peak ALT>1000 IU/l) for each overdose pattern. The development of hepatotoxicity occurred in similar proportions of those treated with each regimen for all patterns of overdose.

For hepatic injury development (

Figure 3-4), 341 patients with hepatic injury (ALT>100) on admission were excluded from the analysis. The proportions developing ALT peak >100 were 4.6% and 4.3% for the SNAP and standard groups, respectively.

Figure 3-5 shows the development of INR>2 after excluding 70 patients who had INR>2 on admission. Comparing the SNAP and standard regimen, proportions were similar for each overdose pattern.

Detailed statistical analysis for each pattern of overdose will be presented separately.

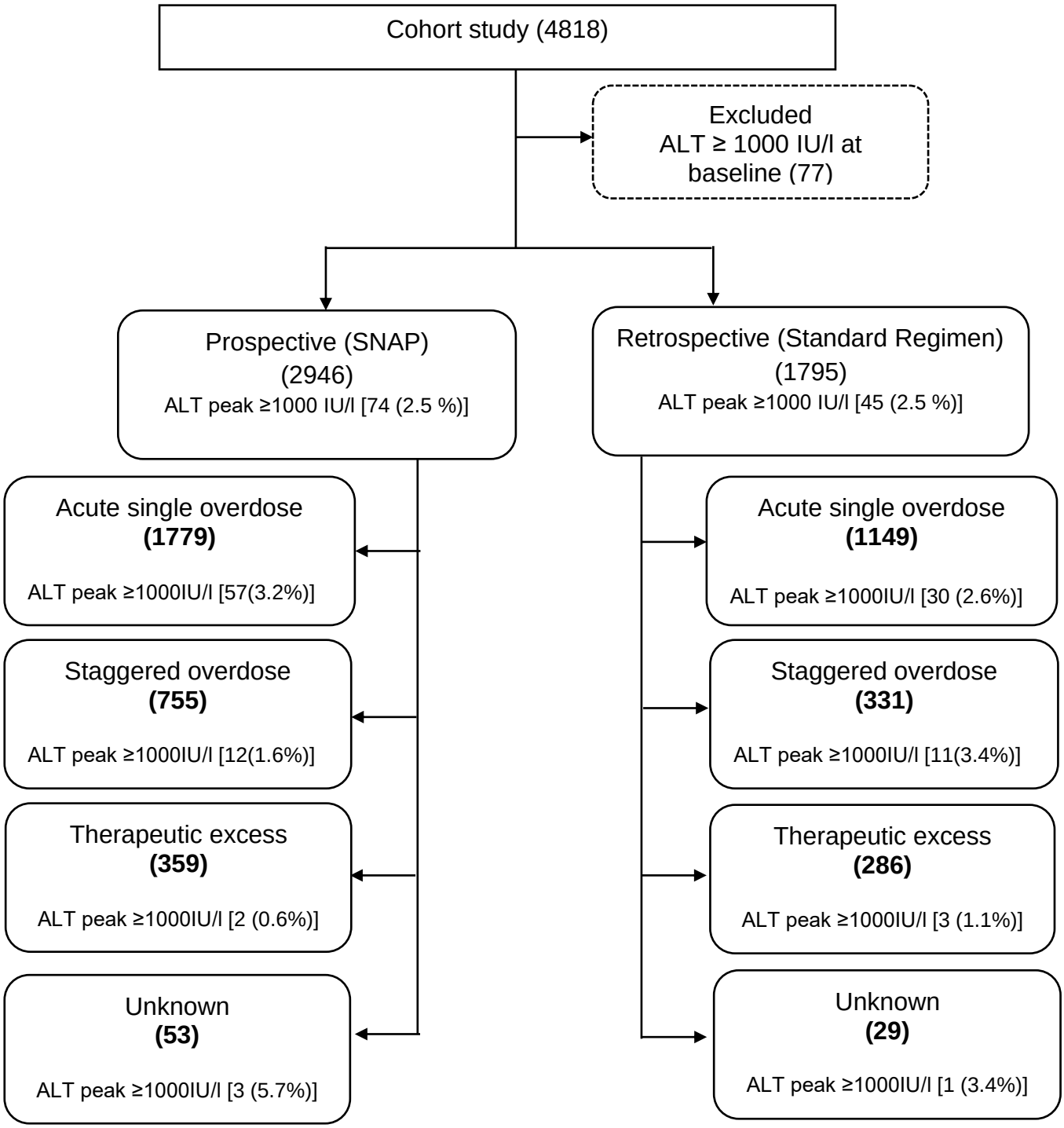


Figure 3-3: The outcomes of ALT peak >1000IU/l for patients treated with SNAP and standard regimen by pattern of overdose

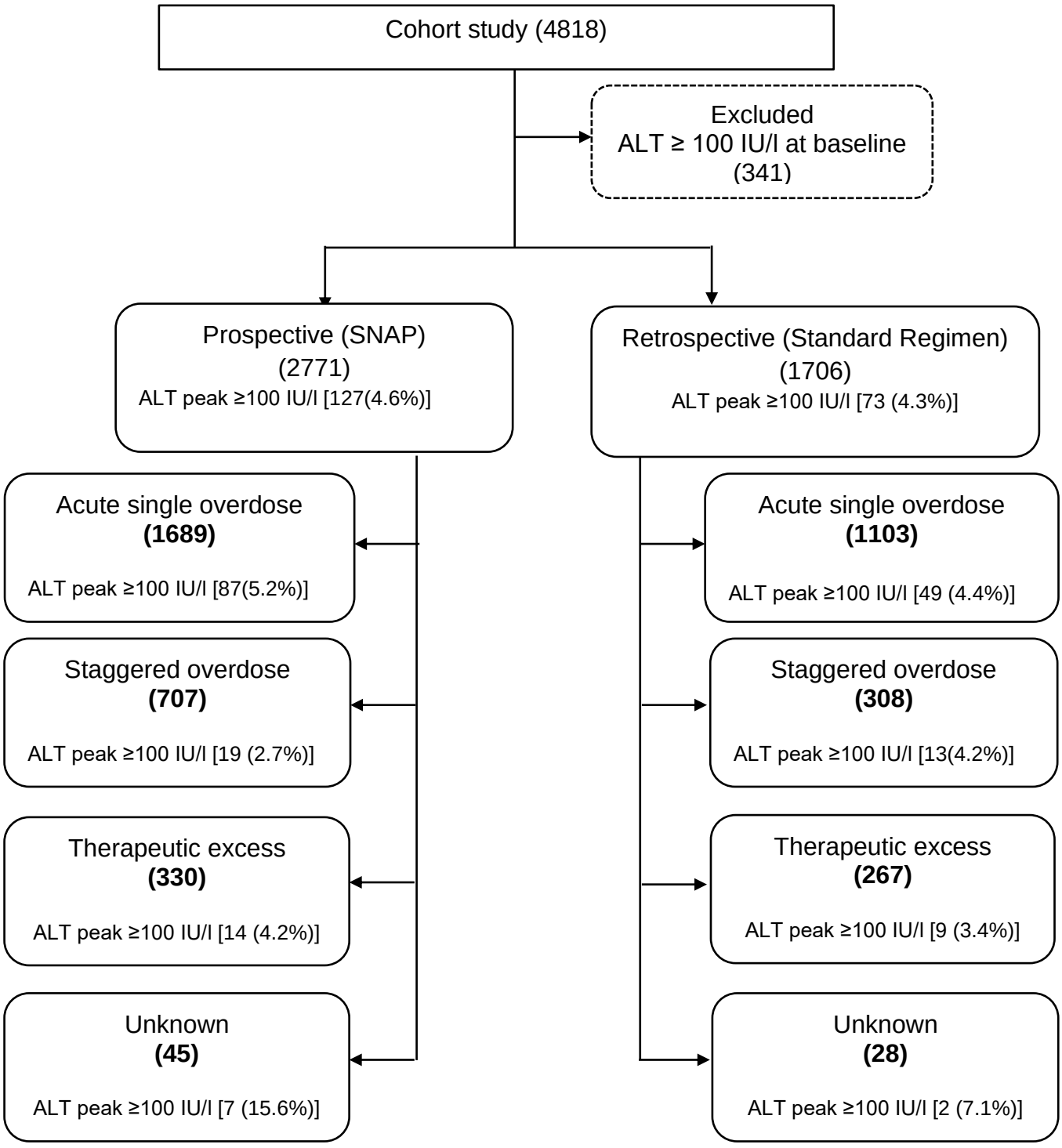


Figure 3-4: The outcome of ALT peak >100IU/l for patients treated with SNAP and standard regimen by pattern of overdose

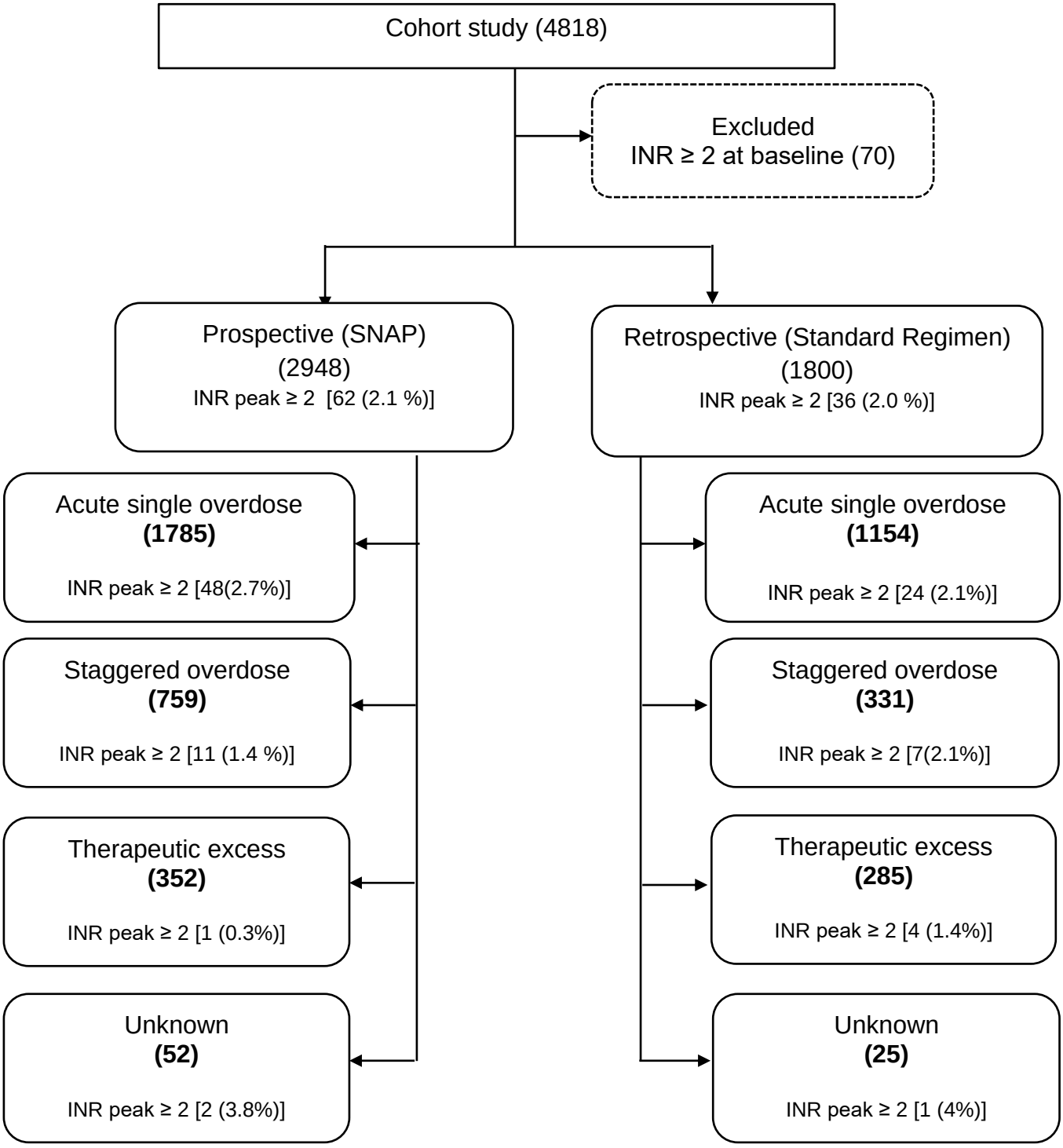


Figure 3-5: The outcomes of INR peak >2 breakdown for patients treated with SNAP and standard regimen and based on pattern of overdose

3.3.1. Acute Single Overdose

Patient characteristics

An overview of clinical characteristics of patients with acute single treated with the SNAP and standard regimens from RVI, STH, and RIE is shown in **Table 3-2**. There is no difference in age, weight, gender, paracetamol dose ingested, admission ALT and APAP*ALT product or time to acetylcysteine treatment between those treated with the SNAP and standard regimens. Of the SNAP participants, 63.4% (1069/1685) received NAC within 8 hours of ingestion compared with 61.1% (604/988) of those treated with the standard regimen(P=0.28). However, the proportion of patients receiving NAC more than 16 hours post-ingestion was significantly higher in the standard 21 h regimen (125/988 (12.7%) compared to the SNAP regimen 162/1685 (9.8%), P=0.013). Another important factor is the paracetamol concentration extrapolated to 4 hours after overdose (nomogram band). The proportion of patients above the 150-nomogram band was significantly greater in those treated with the standard regimen (55.7% vs 49.6, P=0.0024), but the proportion of patients above the 300-nomogram line was significantly higher in those treated with SNAP (137/1673,8.2%) compared to the standard regimen (43/977,4.4%, p=0.0002).

Table 3-2 Characteristics of patients with acute single overdose.

Acute single overdose Factors	SNAP			Standard			Total per regimen [N (%)]		Absolute Difference % (95%CI)	P-value
	Newcastle 894	London 222	Edinburgh 663	Newcastle 260	London 169	Edinburgh 720	**SNAP (1779)**	**Standard (1149)**		
Gender Male No. (%) Female No. (%)	298/894 (33.3) 596/894 (66.7)	81/222(36.5) 141/222 (63.5)	188/663 (28.4) 475/663 (71.6)	103/260 (39.6) 157/260 (60.4)	80/169 (47.3) 89/169 (52.7)	183/720 (25.4) 537/720 (74.6)	567/1779 (31.9) 12121779 (68.1)	366/1149 (31.9) 783/1149 (68.1)	0 (- 3.4 to 3.4)	P=0.513
Age year [median,(IQR)]	27 (21)	27 (27)	30(27)	29(23)	31(27)	29(23)	28(24)	29(23)	Not applicable	P=0.36
Weight (KG) [median,(IQR)]	70 (25)	70 (26)	69.5 (26)	68 (23)	74 (24)	68.5 (23)	70 (25)	69 (23)	Not applicable	P =0.841
Paracetamol dose/kg [median,(IQR)]	228.6 (158.7)	200 (139.6)	214 (150)	264.2 (196.3)	194.1 (167.2)	216.8 (142.9)	222.2 (163)	223.9 (157.9)	Not applicable	P =0.91
ALT admission [median,(IQR)]	19 (18)	20 (17)	18 (16)	19 (18)	21 (18)	17 (16)	18 (17)	18 (17)	Not applicable	P =0.97
ALT admission Normal No. (%) Abnormal No. (%)	735/883 (83.2) 148/883 (16.8)	167/196 (91.3) 29/196 (8.7)	567/661 (85.8) 94/661 (14.2)	209/257 (81.3) 48/257 (18.7)	46/58 (79.3) 12/58 (20.7)	636/716 (88.8) 80/716 (11.2)	1469/1740 (84.4) 271/1740 (15.6)	891/1031 (86.4) 140/1031 (13.6)	-2.0 (- 0.76 to 4.6)	P=0.15
INR admission [median,(IQR)]	1 (0.1)	1 (0.1)	1 (0.2)	1 (0.1)	1 (0.1)	1 (0.2)	1 (0.1)	1 (0.1)	Not applicable	P =0.15
Extrapolated paracetamol at 4 hour [median,(IQR)]	147 (125)	142.8 (110.2)	N/A	156.6 (138.2)	129.7 (136.2)	N/A	143.4 (119)	150.2 (139.2)	Not applicable	P =0.43
Paracetamol× ALT products ≤1500 No. (%) >1500 No. (%)	331/880 (37.6) 549/880 (62.4)	67/195 (34.4) 128/195 (65.6)	211/661 (31.9) 450/661 (68.1)	72/257 (28) 185/257 (72)	28/58(48.3) 30/58 (51.7)	276/715 (38.6) 439/715 (61.4)	609/1736 (35) 1127/1736 (65)	376/1030 (36.5) 654/1030 (63.5)	-1.5 (- 2.17 to 5.2)	P= 0.237
Time to NAC (h) [median,(IQR)]	7 (5)	7 (4)	7 (3)	7 (5)	8 (7)	8 (6)	7 (4)	7.5 (5)	Not applicable	P= 0.056
Time to NAC (h) ≤16 (%) >16 (%)	728/818 (89) 90/818(11)	205/220(93.2) 15/220(6.8)	563/620 (90.8) 57/620 (9.2)	217/245 (88.6) 28/245 (11.4)	47/53 (88.7) 6/53 (11.3)	599/690 (86.8) 91/690 (13.2)	1496/1658 (90.2) 162/1685 (9.8)	863/988 (87.3) 125/988 (12.7)	2.9 (1.2 to 6.2)	P=0.013
Nomogram Band (%) <150 ≥ 150	427/817 (52.3) 390/817 (47.7)	109/215 (50.7) 106/215 (49.3)	308/641 (48) 333/641 (52)	119/253 (47) 134/253 (53)	34/57 (59.6) 23/57 (40.4)	280/667 (42) 387/667 (58)	(844/1673 (50.4) (829/1673 (49.6)	(433/977) (44.3) (544/977) (55.7)	6.1 (2.2 to 10)	P= 0.0024

Outcomes

1. **NAARs**

The proportion of patients who developed NAARs requiring treatment with an antihistamine was significantly higher in the standard regimen compared to the SNAP regimen (1.3% vs 7.9%, p= 0.0001).

Table 3-3: NAARs development in patients with acute overdose

NAARs	SNAP (1779)	Standard (1149)	Absolute Difference (95%CI) P-value
Yes (%)	14/1079 **(1.3)**	25/316 **(7.9)**	6.6 (3.96 to 10.14) P=0.0001
No (%)	1065/1079 **(98.7)**	291/316 **(92.1)**	

2. **Peak ALT**

Table 3-4 shows the distribution of peak ALT <100, 100-1000 in both regimens broken down by time from ingestion to NAC treatment and nomogram band. Peak ALT <100, 100 to 1000, and >1000 occurred in 90.2%, 6.6%, and 3.2% of patients treated with the SNAP regimen and 91.8%, 5.6%, and 2.6% of patients treated with the standard regimen, respectively.

Table 3-4:Patients with acute single overdose developing peak ALT <100, 100-1000, and >1000

Nomogram Band	SNAP					Standard				
	Time to NAC					Time to NAC				
	≤8	8-16	>16	Unknown	Total	≤8	8-16	>16	Unknown	Total
<150	561 **(31.6)**	197 **(11.1)**	64 **(3.6)**	22 **(1.2)**	844 **(47.5)**	273 **(23.9)**	94 **(8.2)**	47 **(4.1)**	17 **(1.5)**	431**(37.8)**
150-300	442 **(24.9)**	181 **(10.2)**	47 **(2.6)**	21 **(1.2)**	691 **(38.9)**	299 **(26.2)**	149 **(13.1)**	39 **(3.4)**	12 **(1.1)**	499**(43.8)**
≥300	44 **(2.5)**	45 **(2.5)**	48 **(2.7)**	0 **(0)**	137 **(7.7)**	14 **(1.2)**	12 **(1.1)**	15 **(1.3)**	1 **(0.1)**	42 **(3.7)**
Unknown	22 **(1.2)**	3 **(0.2)**	3 **(0.2)**	77 **(4.3)**	105 **(5.9)**	16 **(1.4)**	3 **(0.3)**	24 **(2.1)**	125 **(11)**	168 **(14.7)**
Total	1069 **(60.2)**	426 **(24)**	162 **(9.1)**	120 **(6.8)**	1777	602 **(52.8)**	258 **(22.6)**	125 **(11)**	155 **(13.6)**	1140
Peak ALT <100										
<150	544 **(97)**	179 **(90.9**)	50 **(78.1)**	18 **(81.8)**	791 **(93.7)**	262 **(96)**	89 **(94.7)**	44 **(93.6)**	16 **(94.1)**	411 **(95.4)**
150-300	412 **(93.2)**	152 **(84)**	34 **(72.3)**	20 **(95.2)**	618 **(89.4)**	286 **(95.7)**	130 **(87.2)**	34 **(87.2)**	9 **(75)**	459 **(92)**
≥300	38 **(86.4)**	33 **(73.3)**	30 **(62.5)**	0 **(0)**	101 **(73.7)**	11 **(78.6)**	10 **(83.3)**	8 **(53.3)**	1 **(100)**	30 **(71.4)**
Unknown	20 **(90.9)**	3 **(100)**	2 **(66.7)**	67 **(87)**	92 **(87.6)**	16 **(100)**	3 **(100)**	17 **(70.8)**	110 **(88)**	146 **(86.9)**
Total	1014 **(94.9)**	367 **(86.2)**	116 **(71.6)**	105**(87.5)**	1602**(90.2)**	575 **(95.5)**	232 **(89.9)**	103 **(82.4)**	136 **(87.7)**	1046 **(91.8)**
Peak ALT 100-1000										
<150	17 **(3)**	15 **(7.6)**	10 **(15.6)**	4 **(18.2)**	46 **(5.5)**	11**(4)**	5 **(5.3)**	1 **(2.1)**	1 **(5.9)**	18 **(4.2)**
150-300	18 **(4.1)**	17 **(9.4)**	10 **(21.3)**	1 **(4.8)**	46 **(6.7)**	8 **(2.7)**	11 **(7.4)**	3 **(7.7)**	2 **(16.7)**	24 **(4.8)**
≥300	3 **(6.8)**	8 **(17.8)**	5 **(10.4)**	0 **(0)**	16 **(11.7)**	0 **(0)**	1 **(8.3)**	5 **(33.3)**	0 **(0)**	6 **(14.3)**
Unknown	2 **(9.1)**	0 **(0)**	0 **(0)**	8 **(10.4)**	10 **(9.5)**	0 **(0)**	0 **(0)**	7 **(29.2)**	9 **(7.2)**	16 **(9.5)**
Total	40 **(3.7)**	40 **(9.4)**	25 **(15.4)**	13 **(10.8)**	118 **(6.6)**	19 **(3.2)**	17 **(6.6)**	16 **(12.8)**	12 **(7.7)**	64 **(5.6)**
Peak ALT >1000										
<150	0 **(0)**	3 **(1.5)**	4 **(6.3)**	0 **(0)**	7 **(0.8)**	0 **(0)**	0 **(0)**	2 **(4.3)**	0 **(0)**	2 **(0.5)**
150-300	12 **(2.7)**	12 **(6.6)**	3 **(6.4)**	0 **(0)**	27 **(3.9)**	5 **(1.7)**	8 **(5.4)**	2 **(5.1)**	1 **(8.3)**	16 **(3.2)**
≥300	3 **(6.8)**	4 **(8.9)**	13 **(27.1)**	0 **(0)**	20 **(14.6)**	3 **(21.4)**	1 **(8.3)**	2 **(13.3)**	0 **(0)**	6 **(14.3)**
Unknown	0 **(0)**	0 **(0)**	1 **(33.3)**	2 **(2.6)**	3 **(2.9)**	0 **(0)**	0 **(0)**	0 **(0)**	6 **(4.8)**	6 **(3.6)**
Total	15 **(1.4)**	19 **(4.5)**	21 **(13)**	2 **(1.7)**	57 **(3.2)**	8 **(1.3)**	9 **(3.5)**	6 **(4.8)**	7 **(4.5)**	30 **(2.6)**

A. ALT peak >1000 in all acute single overdoses

Table 3-5 shows the breakdown of patients with acute single paracetamol overdose developing hepatotoxicity (peak ALT>1000 IU/l) by hospital, regimen (SNAP and standard), time to NAC and nomogram band. When taking into account time to NAC there was no significant difference in the proportion of patients developing peak ALT>1000 between the SNAP and standard regimen (absolute difference 0.6; 95% CI - 0.7 to 1.8). There were some differences between hospitals with peak ALT>1000 in patients in the Newcastle and London hospitals occurring more frequently in the standard regimen vs the SNAP regimen although this was not statistically significant (3.1% vs 4.3%, P= 0.34, 1.8% vs 3%, P=0.44, respectively). In contrast, ALT peak >1000 in patients in Edinburgh occurred more frequently with the SNAP regimen (3.8% vs 1.9%, 95% CI 0.14 to 3.81, P= 0.032).

Hepatotoxicity occurred less frequently (1.3%) when NAC treatment was commenced within 8 hours of ingestion and was at its highest when NAC treatment commenced more than 16 hours after overdose (4.8%). In patients receiving NAC within 8h of overdose, there was no significant difference in the proportion of patients developing peak ALT >1000 (1.4% SNAP vs 1.3% standard, 95% CI, - 1.3 to 1.2, P= 0.86). Similarly, there was no significant difference in peak ALT>1000 in patients receiving NAC treatment within 8-16 hours even though there were differences by hospital: in Newcastle, significantly lower ALT peak >1000 in SNAP vs standard (1% vs 6.1%, P=0.017) but in Edinburgh, significantly higher peak ALT>1000 in SNAP vs standard regimen (8.1% vs 2.8%, P=0.028). However, for patients treated with NAC more than 16 hours of overdose, there was a higher proportion of ALT peak >1000 with the SNAP vs standard regimen in all 3 hospitals (14.4% vs 10.7%, P=0.6 in Newcastle, 6.7% vs 0% in London, P=0.05, 12.3% vs 3.3% in Edinburgh, P=0.03 respectively). Overall, ALT peak >1000 occurred significantly more frequently with the SNAP regimen compared to the standard regimen (13% vs 4.8%, P=0.018).

The impact of the nomogram band (<150, 150 to 299, and ≥ 300) on the development of ALT peak >1000 is illustrated in **Table 3-5**. When the nomogram band is <150, only 7 patients (0.8%) in the SNAP regimen and 2 patients (0.5%) in the standard regimen developed a peak ALT>1000, with all 9 of these patients receiving NAC more than 8

hours after overdose. The risk of developing hepatotoxicity was higher in the nomogram band>300 but was similar between both regimens.

Binary logistic regression analysis was performed for the outcome of ALT peak >1000 IU/l using each of the following predictor variables: regimen (SNAP, standard), ALT baseline (IU/l) (normal, abnormal), time to NAC, APAP x AT product (≤ 1500, >1500), nomogram bands (<150, ≥ 150), dose (mg)/kg (<300, ≥ 300), age (year) (≤ 30, >30), and weight (kg). Variables which were statistically significant were entered in a multivariate regression model in a forward stepwise manner. This multivariate analysis showed that there was no statistical difference between the two regimens for the outcome of peak ALT>1000 (adjusted OR 1.1, 95% CI 0.6-2.0, p=0.765). Predictors of the development of peak ALT>1000 were admission ALT>50, time to NAC, APAP x AT product>1500, ingested paracetamol dose>300 mg/kg and nomogram band>150. (**Table 3-6**)

Table 3-5: Patients with acute single overdose developing ALT peak >1000

ALT Peak ≥1000 Risk Factor /Location/Regimen	SNAP [N (%)]			Standard [N (%)]			Total per regimen [N (%)]		Absolute Difference % (95%CI)
	Newcastle	London	Edinburgh	Newcastle	London	Edinburgh	SNAP	Conventional	
Acute Overdose	894	222	663	260	169	720	1779	1149	
Time to NAC [N (%)]	28/892 **(3.1)**	4 /222 **(1.8)**	25/663 **(3.8)**	11/258**(4.3)**	5/ 164(3)	14/718(1.9)	57/1777 (3.2)	30/1140 (2.6)	0.6 (- 0.7 to 1.8)
≤8	11/533 **(2.1)**	0/145 **(0)**	4/391 **(1**)	4/150 **(2.7)**	0/31 **(0)**	4/421 **(1)**	15/1069 **(1.4)**	8/602 **(1.3)**	0.1 (- 1.3 to 1.2)
8-16	2/194 **(1)**	3/60 **(5)**	14/172 **(8.1)**	4/66 **(6.1)**	0/15 **(0)**	5/177 **(2.8)**	19/426 **(4.5)**	9/258 **(3.5)**	1 (- 2.4 to 3.9)
>16	13/90 **(14.4)**	1/15 **(6.7)**	7/57 **(12.3)**	3/28 **(10.7)**	0//6 **(0)**	3/91 **(3.3)**	21/162 **(13)**	6/125 **(4.8)**	8.2 (1.4 to 14.8)
U/A	2/75 **(2.7)**	0/2 **(0)**	0/43 **(0)**	0/14 **(0)**	5/112 **(4.5)**	2/29 **(6.9)**	2/120 **(1.7)**	7/155 **(4.5)**	-2.8 (-2.0 to 7.5)
Nomogram Band	28/892 **(3.1)**	4 /222 **(1.8)**	25/663 **(3.8)**	11/258**(4.3)**	5/ 164(3)	14/718(1.9)	57/1777 (3.2)	30/1140 (2.6)	0.6 (- 0.7 to 1.8)
<150	0/427 **(0)**	0/109 **(0)**	7/308 **(2.3)**	1/119 **(0.8)**	0/33 **(0)**	1/279 **(0.4)**	7/844 **(0.8)**	2/431 **(0.5)**	0.3 (- 1.0 to 1.2)
150-300	8/281 **(2.8)**	1/77 **(1.3)**	18/333 **(5.4)**	4/97 **(4.1)**	0/16 **(0)**	12/386 **(3.1)**	27/691 **(3.9)**	16/499 **(3.2)**	0.7 (- 1.4 to 3.0)
≥300	17/108 **(15.7)**	3/29 **(10.3)**	0/0 **(0)**	6/35 **(17.1)**	0/7 **(0)**	0/0 **(0)**	20/137 **(14.6)**	6/42 **(14.3)**	0.3 (-14.1 to 10.5)
N/A	3/76 **(3.9)**	0/7 **(0)**	0/22 **(0)**	0/7 **(0)**	5/108 **(4.6)**	1/53 **(1.9)**	3/105 **(2.9)**	6/168 **(3.6)**	0.7 (- 4.9 to 5.1)

Table 3-6: Binary logistic regression for outcome of ALT peak >1000IU/l in all patients with acute single paracetamol overdose.

Outcome: ALT peak >1000				
Univariate regression analysis	**P=**	**B**	**Odds ratio**	**95% C.I for odds ratio**
Regimen (SNAP)	0.373	0.204	1.226	0.78 to 1.92
Abnormal ALT at baseline	0.0001	2.9	17.8	10.8 to 29.4
Time to NAC	0.0001	0.041	1.042	1.025 to 1.059
APAP*AT>1500	0.0001	1.955	7.066	3.064 to 16.29
Nomogram band ≥150	0.0001	2.0	7.466	3.71 to 15.02
Dose (mg)/kg ≥ 300	0.0001	1.9	6.468	3.89 to 10.75
Age (Years) >30	0.022	0.5	1.659	1.074 to 2.563
Patient Wt. (kg)	0.047	-0.13	0.987	0.97 to 1.0
Multivariate regression analysis				
Regimen (SNAP)	0.744	0.09	1.1	0.61 to 1.98
Abnormal ALT at baseline	0.0001	2.5	12.8	7.02 to 23.4
Time to NAC	0.0001	0.56	1.058	1.029 to 1.089
APAP*AT>1500	0.002	2.3	9.9	2.4 to 40.8
Nomogram band ≥150	0.004	1.2	3.3	1.49 to 7.5
Dose (mg)/kg ≥ 300	0.0001	1.2	3.44	1.92 to 6.3
Age (Year) >30	0.23	-0.35	0.71	0.402 to 1.2

B. ALT peak >100 in all acute single overdoses

Table 3-7 shows the breakdown of patients with acute single paracetamol overdose developing hepatic injury (peak ALT>100 IU/l) by hospital, regimen (SNAP and standard), time to NAC and nomogram band. When taking into account time to NAC there was no significant difference in the proportion of patients developing peak ALT>100 between the SNAP and standard regimen (absolute difference 0.8; 95% CI - 0.8 to 2.4).

There were some differences between hospitals with peak ALT>100 in patients in the Newcastle and London hospitals occurring more frequently in the standard regimen vs the SNAP regimen although this was not statistically significant (4.9% vs 7.3%, P= 0.14, 2.5% vs 6%, P=0.08, respectively). In contrast, ALT peak >100 in patients in Edinburgh occurred more frequently with the SNAP regimen (6.3% vs 3%, 95% CI 1.03 to 5.7, P= 0.004).

In general, hepatotoxicity occurred less frequently (2.5%) when NAC treatment was commenced within 8 hours of ingestion and was at its highest when NAC treatment commenced more than 16 hours after overdose (7.2%). In patients receiving NAC within 8 hours of overdose, there was no significant difference in the proportion of patients developing peak ALT >100 (2.8% SNAP vs 2.5% standard, 95% CI, - 1.5 to 1.8, P= 0.72). Similarly, there was no significant difference in peak ALT>100 in patients receiving NAC treatment within 8-16 hours even though there were differences by hospital: in Newcastle, no significant difference in ALT peak >100 in SNAP and standard (7.5% vs 7.7%, P=0.95) but in Edinburgh, significantly higher peak ALT>100 in SNAP vs standard regimen (12.4% vs 5.9%, P=0.04). However, for the group of patients treated with NAC more than 16 hours of overdose, ALT peak >100 occurred more frequently with the SNAP regimen compared to the standard regimen but was not statistically significant, (11.5% vs 7.2%, P=0.26), although in Edinburgh, there was a significantly higher proportion of patients with ALT peak >100 with the SNAP vs standard regimen (17.4% vs 4.8%, P=0.02).

The impact of the nomogram band (<150, 150 to 299, and ≥ 300) on development of ALT peak >100 is illustrated in **Table 3-7**. When the nomogram band is <150, 22 patients (2.6%) in the SNAP regimen and 4 patients (1.0%) in the standard regimen developed peak ALT>100, 24 patients had abnormal ALT at admission, and ALT peak

less than 200IU/l. Two patients (one patient in standard and 1 patient in SNAP) had normal ALT at admission, ALT peak >500IU/l, but time to NAC greater than 8 hours. The risk of developing hepatic injury was higher in the nomogram band>300 but not significantly different between the two regimens.

Binary logistic regression analysis was performed for the outcome of ALT peak >100 IU/l using each of the following predictor variables: regimen (SNAP, standard), ALT baseline (IU/l) (normal, abnormal), time to NAC, APAP x AT product (≤ 1500, >1500), nomogram bands (<150, ≥ 150), dose (mg)/kg (<30, ≥ 300), age (year) (≤ 30, >30), and weight (kg). Variables that were statistically significant were entered in a multivariate regression model in a forward stepwise manner. This multivariate analysis showed that there was no statistical difference between the two regimens for the outcome of peak ALT>100 (adjusted OR 1.22, 95% CI 0.79-1.89, p=0.38). Predictors of development of peak ALT>100 were admission ALT>50, time to NAC, ingested paracetamol dose>300 mg/kg and nomogram band>150 (**Table 3-8**).

Table 3-7: Patients with acute single overdose developing ALT peak >100

ALT Peak ≥ 100 Risk Factor /Location/Regimen	SNAP [N (%)]			Standard [N (%)]			Total per regimen [N (%)]		Absolute Difference % (95%CI)
	Newcastle	London	Edinburgh	Newcastle	London	Edinburgh	SNAP	Conventional	
Acute Overdose	852	215	622	246	167	690	1689	1103	
Time to NAC [N (%)]	42/852 **(4.9)**	6 /215 **(2.8)**	39/622 **(6.3)**	18/246**(7.3)**	10/ 167**(6)**	21/690**(3)**	87/1689 **(5.2)**	49/1103 **(4.4)**	0.8 (- 0.8 to 2.4)
≤8	17/523 **(3.3)**	2/142 **(1.4)**	10/377 **(2.7**)	9/146 **(6.2)**	0/32 **(0)**	6/414 **(1.4)**	29/1042 **(2.8)**	15/592 **(2.5)**	0.3 (- 1.5 to 1.8)
8-16	14/187 **(7.5)**	2/56 **(3.6)**	20/161 **(12.4)**	5/65 **(7.7)**	0/13 **(0)**	10/169 **(5.9)**	36/404 **(8.9)**	15/247 **(6.1)**	2.8 (- 1.6 to 6.8)
>16	5/70 **(7.1)**	2/15 **(13.3)**	8/46 **(17.4)**	4/22 **(18.2)**	0//6 **(0)**	4/83 **(4.8)**	15/131 **(11.5)**	8/111 **(7.2)**	4.3 (-3.4 to 11.8)
U/A	6/72 **(8.3)**	0/2 **(0)**	1/38 **(2.6)**	0/13 **(0)**	10/116 **(8.6)**	1/24 **(4.2)**	7/112 **(6.3)**	11/153 **(7.2)**	-0.9 (-5.9 to 7.0)
Nomogram Band	42/852 **(4.9)**	6 /215 **(2.8)**	39/622 **(6.3)**	18/246**(7.3)**	10/ 167**(6)**	21/690**(3)**	87/1689 **(5.2)**	49/1103 **(4.4)**	0.8 (- 0.8 to 2.4)
<150	7/416 **(1.7)**	1/107 **(1.0)**	14/308 **(4.5)**	3/113 **(2.7)**	0/33 **(0)**	1/271 **(0.4)**	22/831 **(2.6)**	4/417 **(1.0)**	1.6 (- 0.1 to 3.1)
150-300	18/275 **(6.5)**	2/75 **(2.7)**	25/314 **(7.8)**	9/98 **(9.2)**	0/15 **(0)**	19/375 **(5.1)**	45/664 **(6.8)**	28/488 **(5.7)**	1.1 (- 1.8 to 3.9)
≥300	11/89 **(12.4)**	3/26 **(7.7)**	0/0 **(0)**	5/29 **(17.2)**	0/7 **(0)**	0/0 **(0)**	14/115 **(12.2)**	5/36 **(13.9)**	-1.7(-13.6 to 12.1)
N/A	6/72 **(8.3)**	0/7 **(0)**	0/0 **(0)**	1/6 **(16.7)**	10/112 **(8.9)**	1/44 **(2.3)**	6/79 **(7.6)**	12/162 **(7.4)**	0.2 (- 6.3 to 8.8)

Table 3-8: Binary logistic regression for outcome of ALT peak >100IU/l in all patients with acute single paracetamol overdose

Outcome: **ALT peak >100**				
Univariate regression analysis	**P=**	**B**	**Odds ratio**	**95% C.I for odds ratio**
Regimen (SNAP)	0.42	0.15	1.16	0.81 to 1.66
Abnormal ALT at baseline	0.0001	1.9	6.6	4.5 to 9.7
Time to NAC	0.0001	0.032	1.033	1.01 to 1.05
APAP*AT>1500	0.001	0.76	2.14	1.4 to 3.3
Nomogram band ≥150	0.0001	1.3	3.6	2.3 to 5.6
Dose (mg)/kg ≥ 300	0.0001	1.5	4.7	3.2 to 6.9
Age (Years) >30	0.07	0.3	1.4	0.98 to 1.95
Patient Wt. (kg)	0.47	-0.004	0.99	0.98 to 1.006
Multivariate regression analysis				
Regimen (SNAP)	0.38	0.19	1.22	0.79 to 1.89
Abnormal ALT at baseline	0.0001	1.65	5.2	3.29 to 8.26
Time to NAC	0.001	0.04	1.044	1.02 to 1.07
APAP*AT>1500	0.22	0.390	1.5	0.79 to 2.73
Nomogram band ≥150	0.003	0.82	2.26	1.32 to 3.84
Dose (mg)/kg ≥ 300	0.0001	1.12	3.07	1.97 to 4.77

C. INR peak >2 in all acute single overdoes

Table 3-9 shows the breakdown of patients with acute single paracetamol overdose developing hepatic synthetic dysfunction (peak INR>2) by hospital, regimen (SNAP and standard), time to NAC and nomogram band. When taking into account time to NAC there was no significant difference in the proportion of patients developing peak INR>2 between the SNAP and standard regimens (absolute difference 0.6; 95% CI -0.6 to 1.7). Correspondingly, all three hospitals did not report any differences with peak INR>2 in patients with the standard and the SNAP regimens (2.5% vs 1.9%, P= 0.58, 0.9% vs 1.8%, P=0.44, 3.6% vs 2.2%, P=0.12, in Newcastle, London and Edinburgh, respectively). In general, peak INR>2 occurred less frequently (1.3%) when NAC treatment was commenced within 8 hours of ingestion and was at its highest when NAC treatment commenced more than 16 hours after overdose (4.7%). In patients receiving NAC within 8h of overdose, there was no significant difference in the proportion of patients developing peak INR >2 (1.8% SNAP vs 1.3% standard, 95% CI, - 1.3 to 1.2, P= 0.44). Similarly, there was no significant difference in peak INR>2 in patients receiving NAC treatment within 8-16 hours, and more than 16 hours, as well as in each of the three hospitals. The impact of the nomogram band (<150, 150 to 299, and ≥ 300) on development of INR peak >2 is illustrated in **Table 3-9**. When the nomogram band is <150, only 7 patients (0.8%) in the SNAP regimen and 2 patients (0.5%) in the standard regimen developed INR peak >2, all 9 patients had APAP x AT product more than 1500. The risk of developing hepatotoxicity was higher in the nomogram band>300 but was similar after use of each regimen.

Binary logistic regression analysis was performed for the outcome of INR peak >2 using each of the following predictor variables: regimen (SNAP, standard), ALT baseline (IU/l) (normal, abnormal), time to NAC, APAP x AT product (≤ 1500, >1500), nomogram bands (<150, ≥ 150), dose (mg)/kg (<300, ≥ 300), age (year) (≤ 30, >30), and weight (kg). Variables which were statistically significant were entered in a multivariate regression model in a forward stepwise manner. This multivariate analysis showed no statistical difference between the two regimens for the outcome of peak INR >2 (adjusted OR 1.4, 95% CI 0.7-2.5, p=0.4). Predictors of development of peak INR>2 were admission ALT>50, APAP x AT product>1500, ingested paracetamol dose>300 mg/kg and nomogram band>150 (**Table** 3-10).

Table 3-9: Patients with acute single overdose developing INR peak >2

INR Peak > 2 Risk Factor /Location/Regimen	SNAP [N (%)]			Standard [N (%)]			Total per regimen [N (%)]		Absolute Difference % (95%CI)
	Newcastle	London	Edinburgh	Newcastle	London	Edinburgh	SNAP	Conventional	
Acute Overdose	897	222	666	260	169	725	1785	1154	
Time to NAC [N (%)]	22/897 **(2.5)**	2 /222 **(0.9)**	24/666 **(3.6)**	5/260**(1.9)**	3/169**(1.8)**	16/725**(2.2)**	48/1785 **(2.7)**	24/1154 **(2.1)**	0.6 (- 0.6 to 1.7)
≤8	11/531 **(2.1)**	0/145 **(0)**	8/388 **(2.1**)	3/149 **(2.0)**	0/32 **(0)**	5/422 **(1.2)**	19/1064 **(1.8)**	8/603 **(1.3)**	0.5 (- 1.3 to 1.2)
8-16	1/195 **(0.5)**	1/60 **(1.7)**	9/171 **(5.3)**	1/67 **(1.5)**	0/15 **(0)**	3/177 **(1.7)**	11/426 **(2.6)**	4/259 **(1.5)**	1 (- 0.9 to 1.7)
>16	9/94 **(9.6)**	1/15 **(6.7)**	6/61 **(9.8)**	1/28 **(3.6)**	0//6 **(0)**	5/95 **(5.3)**	16/170 **(9.4)**	6/129 **(4.7)**	4.7 (-1.5 to 10.6)
U/A	1/77 **(1.3)**	0/2 **(0)**	1/46 **(2.2)**	0/16 **(0)**	3/116 **(2.6)**	3/31 **(6.7)**	2/125 **(1.6)**	6/163 **(3.7)**	-2.1 (-2.4 to 6.4)
Nomogram Band	22/897 **(2.5)**	2 /222 **(0.9)**	22/644 **(3.4)**	5/260**(1.9)**	3/ 169**(1.8)**	16/725**(2.2)**	46/1763 **(2.6)**	24/1154 **(2.1)**	0.5 (- 0.7 to 1.6)
<150	2/426 **(0.5)**	0/109 **(0)**	5/310 **(1.6)**	0/120 **(0)**	0/34 **(0)**	2/280 **(0.7)**	7/845 **(0.8)**	2/434 **(0.5)**	0.3 (- 1.0 to 1.2)
150-300	7/281 **(2.5)**	0/77 **(0)**	17/334 **(5.1)**	0/97 **(0)**	0/16 **(0)**	11/387 **(2.8)**	24/692 **(3.5)**	11/500 **(2.2)**	1.3 (- 0.7 to 3.2)
≥300	12/112 **(10.7)**	2/29 **(6.9)**	0/0 **(0)**	5/36 **(13.9)**	0/7 **(0)**	0/0 **(0)**	14/141 **(9.9)**	5/43 **(11.6)**	-1.7 (-7.3 to 15.1)
N/A	1/78 **(1.3)**	0/7 **(0)**	0/0 **(0)**	0/7 **(0)**	3/112 **(2.7)**	3/58 **(5.2)**	1/85 **(1.2)**	6/177 **(3.4)**	-2.2 (- 3.3 to 6.1)

Table 3-10**: Binary logistic regression for outcome of INR peak >2 in all patients with acute single paracetamol overdose**

Outcome: **INR peak >2**				
Univariate regression analysis	**P=**	**B**	**Odds**	**95% C.I for odds**
Regimen (SNAP)	0.32	0.25	1.29	0.78 to 2.1
Abnormal ALT at baseline	0.0001	2.2	9.2	5.6 to 15.2
Time to NAC	0.0001	0.03	1.03	1.01 to 1.05
APAP*AT>1500	0.001	2.2	9.13	3.3 to 25.1
Nomogram band ≥150	0.0001	1.7	5.7	2.8 to 11.67
Dose (mg)/kg ≥ 300	0.0001	1.6	5.2	3.04 to 8.8
Age (Years) >30	0.012	0.62	1.86	1.14 to 3.01
Patient Wt. (kg)	0.07	-0.013	0.99	0.97 to 1.001
Multivariate regression analysis				
Regimen (SNAP)	0.38	0.28	1.38	0.7 to 2.5
Abnormal ALT at baseline	0.0001	1.88	6.59	3.5 to 12.2
Time to NAC	0.054	0.02	1.02	1.0 to 1.05
APAP*AT>1500	0.013	1.6	4.97	1.4 to 217.7
Nomogram band ≥150	0.01	1.1	2.9	1.3 to 6.5
Dose (mg)/kg ≥ 300	0.003	0.92	2.5	1.4 to 4.6
Patient Wt. (kg)	0.97	-0.01	0.99	0.55 to 1.8

D. ALT peak >1000 after delayed NAC treatment

Figure 3-6 compares the cumulative proportions of peak ALT >1000 vs time to NAC between the SNAP and standard regimens. The incidence of hepatotoxicity appears to be similar when NAC is administered 12 hours or less after paracetamol ingestion but appears to increase more in the SNAP group beyond 12 hours.

As shown in **Table 3-5**, development of ALT peak >1000 appears significantly more commonly with the SNAP regimen compared to the standard regimen in patients treated more than 16h post-ingestion. The clinical characteristics of this group of patients is shown in **Table 3-11**.There were no significant differences between those treated with each of the 2 regimens.

In patients treated more than 16h post-ingestion (**Table 3-12**), there was a statistically significantly increased risk of developing peak ALT>1000 with the SNAP regimen (unadjusted OR 2.954, 95% CI 1.15 to 7.55, P=0.024); however, when other predictor variables are entered into the regression model, this was no longer statistically significant (adjusted OR 1.3, 95% CI 0.33 to 5.16, P= 0.69). Predictors of peak ALT>1000 were: abnormal ALT at baseline, APAP*AT product>1500, nomogram band >150, and dose ≥300 mg/kg.

In patients treated within 16h of paracetamol ingestion **(Table 3-13**), there was no statistically significant difference in the occurrence of peak ALT >1000 between the SNAP and standard regimens (adjusted OR 1.1, 95% CI 0.55 to 2.2, P= 0.77).

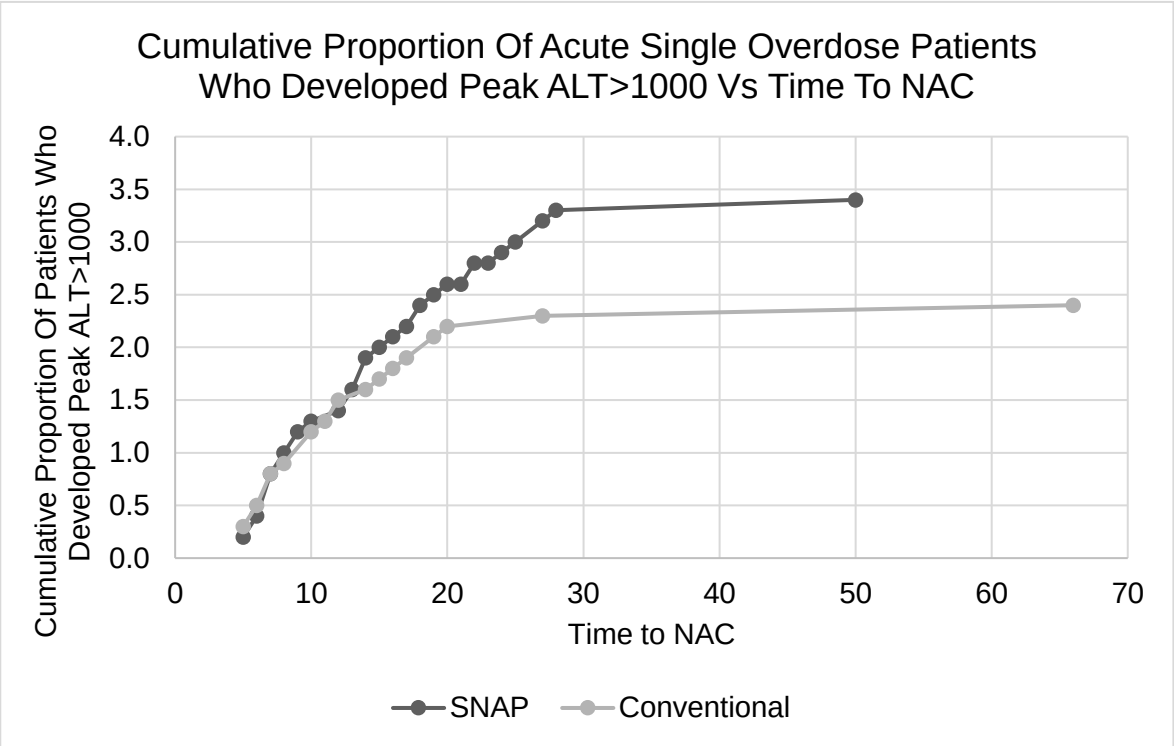


Figure 3-6: Cumulative proportion of patients with acute single overdose who develop peak ALT>1000 with each NAC regimen

Table 3-11: Demographic data of ALT peak >1000 IU/l patients with time to NAC >16 hours of acute single overdose

Factors	SNAP			Standard			SNAP Total (162)	Standard Total (125)	Absolute Difference % (95%CI)	P-value
	Newcastle 90	London 15	Edinburgh 57	Newcastle 28	London 6	Edinburgh 91				
Gender Male (%) Female (%)	37/90 (41.1) 53/90 (58.9)	10/15 (66.7) 5/15 (33.3)	19/57 (33.3) 38/57 (66.7)	12/28 (42.9) 16/28 (57.1)	3/6 (50) 3/6 (50)	25/91 (27.5) 66/91 (72.5)	66/162 (40.7) 96/162 (59.3)	40/125 (32) 85/125 (68)	8.7 (-2.5 to 19.5)	
Age year [median,(IQR)]	30 (26)	35 (30)	35 (33)	37 (32)	29 (46)	23 (24)	31(29)	28 (28)	Not applicable	P=0.3
Weight (KG) [median,(IQR)]	70 (25)	74 (28)	66 (29)	65 (24)	57.8 (22)	70 (20)	70 (25)	68 (22)	Not applicable	P= 0.76
Paracetamol dose/kg [median,(IQR)]	214 (182.4)	226 (360)	219 (161)	244 (233)	226 (333)	202.5 (153)	219.5 (178.8)	214.3 (144.8)	Not applicable	P=0.98
ALT admission [median,(IQR)]	28 (72)	27.5 (26)	24 (44)	33 (76)	16.5 (3)	21 (32)	27 (62)	21 (31)	Not applicable	P=0.14
ALT admission Normal No. (%) Abnormal No. (%)	58/90 (64.4) 32/90 (35.6)	9/13 (69.29) 4/13 (30.8)	40/57 (70.2) 17/57 (29.8)	17/28 (60.7) 11/28 (39.3)	5/6 (83.3) 1/6 (16.7)	73/91 (80.2) 18/91 (19.8)	107/160 (66.9) 53/160 (33.1)	95/125 (76) 30/125 (24)	9.1 (-1.6 to 19.2)	P=0.093
INR admission [median,(IQR)]	1.1 (0.2)	1.0 (0.1)	1.0 (0.2)	1 (0.2)	1 (0.20	1 (0.1)	1.0 (0.2)	1 (0.1)	Not applicable	P= 0.4
Extrapolated paracetamol at 4h [median,(IQR)]	370 (2513)	149 (573)	N/A	134.5 (872)	235 (5792)	N/A	311 (2469)	142.5 (829)	Not applicable	P=0.84
Paracetamol× ALT product ≤1500 No. (%) >1500 No. (%)	64/89 (71.9) 25/89 (28.1)	9/12 (75) 3/12 (25)	43/57 (75.4) 14/57 (24.6)	19/28 (67.9) 9/28 (32.1)	6/6 (100) 0/6 (0)	72/90 (80) 18/90 (20)	116/158 (73.4) 42/158 (26.6)	97/124 (78.2) 27/124 (21.8)	4.8 (-5.4 to 14.5)	P=0.35
Time to NAC (h) [median,(IQR)]	22 (9)	20.5 (7)	21.6 (6)	23 (9)	22 (15)	23 (10)	22 (8)	22 (8)	Not applicable	P=0.75
Nomogram Band(%) <150 ≥ 150	31/89 (34.8) 58/89 (65.2)	6/13 (46.2) 7/13 (53.8)	27/57 (47.4) 30/57 (52.6)	15/27 (55.6) 12/27 (44.4)	3/6 (50) 3/6(50)	29/68 (42.6) 39/68 (57.4)	64/159 (40.3) 95/159 (59.7)	47/101 (46.5) 54/101 (53.5)	6.2 (- 6.0 to 18.3)	

Table 3-12: Binary logistic regression of ALT peak >1000IU/l in patients with acute single overdose treated with NAC >16h post-ingestion

Time to NAC >16	Outcome: ALT peak >1000			
Univariate regression analysis	**P=**	**B**	**Odds ratio**	**95% C.I for Odds ratio**
Regimen (SNAP)	0.024	1.08	2.954	1.15 to 7.55
Abnormal ALT at baseline	0.0001	4.5	91.68	12.17 to 690.3
Time to NAC	0.714	-0.006	0.994	0.96 to 1.028
APAP*AT>1500	0.0001	4.03	56.267	12.84 to 246.67
Nomogram band ≥150	0.039	0.99	2.713	1.051 to 7.001
Dose (mg)/kg ≥ 300	0.0001	1.9	6.711	2.75 to 16.36
Age (Year) >30	0.027	0.97	2.645	1.12 to 6.26
Patient Wt. (kg)	0.26	-0.13	0.987	0.964 to 1.01
Multivariate regression analysis				
Regimen (SNAP)	0.69	0.27	1.31	0.33 to 5.16
Abnormal ALT at baseline	0.003	3.5	33.9	3.3 to 350.1
APAP*AT>1500	0.001	5.2	190.3	9.3 to 3786.8
Nomogram band ≥150	0.029	-3.14	0.04	0.003 to 0.72
Dose (mg)/kg ≥ 300	0.042	1.4	4.1	1.05 to 15.67
Age (Year) >30	0.25	-0.84	0.433	0.1 to 1.8

Table 3-13: Binary logistic regression of ALT peak >1000IU/l in patients with acute single overdose treated with NAC ≤ 16h post-ingestion

Time to NAC ≤ 16	Outcome: ALT peak >1000			
Univariate regression analysis	**P=**	**B**	**odds ratio**	**95% C.I for odds ratio**
Regimen (SNAP)	0.63	0.14	1.154	0.641 to 2.078
Abnormal ALT at baseline	0.001	2.37	10.75	6.04 to 19.14
Time to NAC	0.0001	0.21	1.227	1.123 to 1.331
APAP*AT>1500	0.001	2.34	10.41	2.52 to 42.96
Nomogram band ≥150	0.0001	2.76	15.775	4.89 to 50.79
Dose (mg)/kg ≥ 300	0.0001	1.97	7.16	3.67 to 14.0
Age (Year) >30	0.47	0.21	1.227	0.704 to 2.137
Patient Wt. (kg)	0.279	-0.009	0.991	0.975 to 1.007
Multivariate regression analysis				
Regimen (SNAP)	0.77	0.1	1.11	0.55 to 2.21
Abnormal ALT at baseline	0.0001	2.1	8.5	4.27 to 17.01
Time to NAC	0.0001	0.21	1.23	1.12 to 1.37
APAP*AT>1500	0.13	1.2	3.3	0.71 to 15.8
Nomogram band ≥150	0.002	1.99	7.3	2.13 to 25.2
Dose (mg)/kg ≥ 300	0.0001	1.35	3.8	1.8 to 7.9

E. ALT peak >100 after delayed NAC treatment

Figure 3-7 shows the cumulative proportions of peak ALT >100 vs time to NAC in comparing the SNAP and standard regimen. The incidence of hepatic injury appears to be similar when NAC is administered 12 hours or less from ingestion but appears to be higher in the SNAP group beyond 12 hours. However, **Table 3-7** shows no significant difference in development of ALT peak >100 in the SNAP and standard regimen in patients treated whether before or after 16h post-ingestion. The clinical characteristics of this group of patients is shown in **Table 3-14**. There was a significantly higher proportion of female presents in the standard regimen group

compared the SNAP regimen. All other factors were not significant different between the 2 regimens.

In patients treated more than 16h post-ingestion (**Table** 3-15), there was no statistical difference in development of peak ALT>100 in univariate regression analysis between SNAP and the standard regimens (unadjusted OR 1.67, 95% CI 0.68 to 4.09, P=0.27). When other predictor variables are entered into the regression model, abnormal ALT at baseline was a significant predictor for ALT peak >100 in late presenters (adjusted OR 9.2, 95% CI 3.15 to 26.9, P= 0.0001).

In patients treated within 16h post-ingestion (**Table 3-16**), the occurrence of peak ALT >100 demonstrated no statistical difference in SNAP group (adjusted OR 1.35, 95% CI 0.82 to 2.22, P= 0.24).

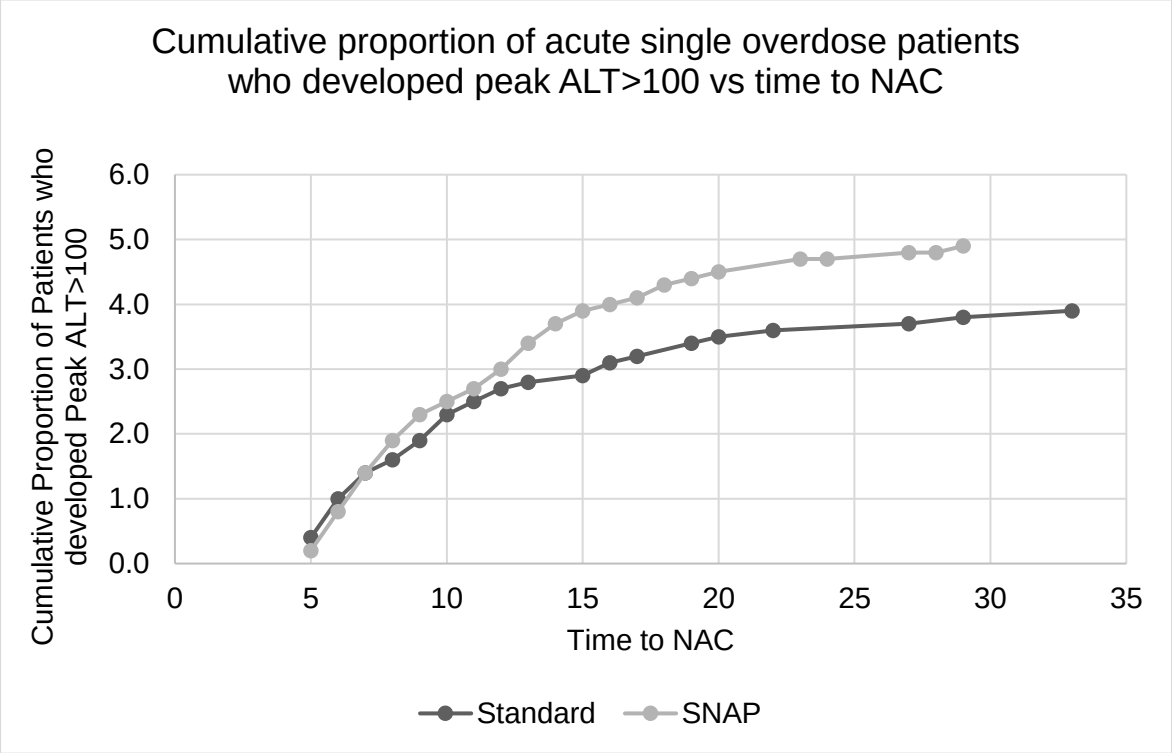


Figure 3-7: Cumulative proportion of patients with acute single overdose who develop peak ALT>100 with each NAC regimen

Table 3-14: Demographic data of ALT peak >100 IU/l patients with time to NAC >16 hours of acute single overdose

Factors	SNAP			Standard			SNAP Total (131)	Standard Total (111)	Absolute Difference % (95%CI)	P-value
	Newcastle 70	London 15	Edinburgh 46	Newcastle 22	London 6	Edinburgh 83				
Gender Male (%) Female (%)	30/70 (42.9) 40/70 (57.1)	10/15 (66.7) 5/15 (33.3)	15/46 (32.6) 31/46 (67.4)	8/22 (36.4) 14/22 (63.6)	3/6 (50) 3/6 (50)	20/83(24.1) 63/83 (75.9)	55/131 (42) 76/131 (58)	31/111 (27.9) 80/111 (72.1)	14.1 (2.0 to 25.5)	P=0.02
Age year [median,(IQR)]	29 (23)	35 (30)	32.5 (36)	33 (33)	29 (46)	23 (21)	30(29)	23 (23)	Not applicable	P=0.16
Weight (KG) [median,(IQR)]	70 (30)	74 (28)	64.5 (30)	65 (21)	57.8 (22)	71 (20)	71.5 (26)	64 (21)	Not applicable	P= 0.56
Paracetamol dose/kg [median,(IQR)]	188.9 (129.8)	226 (360)	206 (119)	228.6 (271)	226 (333)	190.5 (138.6)	191.2 (144.8)	226.7 (199.9)	Not applicable	P=0.57
ALT admission [median,(IQR)]	22 (23)	27.5 (26)	20 (21)	24 (27)	16.5 (3)	18 (14)	22 (22)	19.5 (19)	Not applicable	P=0.53
ALT admission Normal No. (%) Abnormal No. (%)	58/70 (82.9) 12/70 (17.1)	9/13 (69.29) 4/13 (30.8)	40/46 (87) 6/46 (13)	17/22 (77.3) 5/22 (22.7)	5/6 (83.3) 1/6 (16.7)	73/83 (88) 10/83 (12)	107/129 (82.9) 22/129 (17.1)	95/111 (85.6) 16/111 (14.4)	2.7 (-6.8 to 11.8)	P=0.57
INR admission [median,(IQR)]	1.0 (0.2)	1.0 (0.1)	1.1 (0.2)	1 (0.1)	1 (0.2)	1 (0.1)	1.0 (0.1)	1 (0.1)	Not applicable	P= 0.4
Extrapolated paracetamol at 4 h [median,(IQR)]	183.4 (691)	149.2 (434)	N/A	103.7 (557)	234.8 (5792)	N/A	153.3 (414.6)	105.9 (581.1)	Not applicable	P=0.37
Paracetamol× ALT products ≤1500 No. (%) >1500 No. (%)	60/70 (85.7) 10/70 (14.3)	9/12 (75) 3/12 (25)	40/46 (87) 6/46 (13)	17/22 (77.3) 5/22 (22.7)	6/6 (100) 0/6 (0)	69/83 (83.1) 14/83 (16.9)	109/128 (85.2) 19/128 (14.8)	92/111 (82.9) 19/111 (17.1)	2.3 (-6.9 to 11.8)	P=0.62
Time to NAC (h) [median,(IQR)]	22 (9)	20.5 (7)	20.9 (6)	20 (7)	22 (15)	21 (6)	21.5 (8)	20 (8)	Not applicable	P=0.79
Nomogram Band (%) <150 ≥ 150	30/70 (42.9) 40/70 (57.1)	6/13 (46.2) 7/13 (53.8)	22/46 (47.8) 24/46 (52.2)	14/21 (66.7) 7/21 (33.3)	3/6 (50) 3/6(50)	28/65 (43.1) 37/65 (56.9)	58/129 (45) 71/129 (55)	45/92 (48.9) 47/92 (51.1)	3.9 (- 9.3 to 16.9)	P=0.57

Table 3-15**: Binary logistic regression of ALT peak >100 IU/l in patients with acute single overdose treated with NAC >16h post-ingestion**

Time to NAC >16	Outcome: ALT peak >100			
Univariate regression analysis	**P=**	**B**	**Odds ratio**	**95% C.I for Odds ratio**
Regimen (SNAP)	0.27	0.51	1.67	0.68 to 4.09
Abnormal ALT at baseline	0.0001	2.5	12.5	4.9 to 31.9
Time to NAC	0.31	-0.035	0.97	0.90 to 1.03
APAP*AT>1500	0.003	1.4	4.14	1.6 to 10.4
Nomogram band ≥150	0.72	0.17	1.18	0.48 to 2.9
Dose (mg)/kg ≥ 300	0.03	1.03	2.8	1.1 to 7.03
Age (Years) >30	0.52	-0.3	0.75	0.3 to 1.8
Patient Wt. (kg)	0.24	-0.02	0.99	0.96 to 1.01
Multivariate regression analysis				
Regimen (SNAP)	0.33	0.51	1.66	0.59 to 4.64
Abnormal ALT at baseline	0.0001	2.22	9.2	3.15 to 26.9
APAP*AT>1500	0.34	0.56	1.8	0.55 to 5.6
Dose (mg)/kg ≥ 300	0.74	0.18	1.2	0.4 to 3.59

Table 3-16: Binary logistic regression of ALT peak >100 IU/l in patients with acute single overdose treated with NAC ≤ 16h post-ingestion

Time to NAC ≤16	Outcome: ALT peak >100			
Univariate regression analysis	**P=**	**B**	**Odds**	**95% C.I for odds**
Regimen (SNAP)	0.29	0.23	1.26	0.8 to 1.96
Abnormal ALT at baseline	0.0001	1.7	5.4	3.4 to 8.5
Time to NAC	0.0001	0.18	1.2	1.13 to 1.28
APAP*AT>1500	0.001	1.3	3.8	1.9 to 7.4
Nomogram band ≥150	0.0001	1.6	5.02	2.9 to 8.65
Dose (mg)/kg ≥ 300	0.0001	1.7	5.3	3.4 to 8.4
Age (Years) >30	0.103	0.34	1.4	0.93 to 2.1
Patient Wt. (kg)	0.63	-0.003	0.99	0.98 to 1.006
Multivariate regression analysis				
Regimen (SNAP)	0.24	0.3	1.35	0.82 to 2.22
Abnormal ALT at baseline	0.0001	1.3	3.8	2.2 to 6.6
Time to NAC	0.0001	0.27	1.3	1.2 to 1.4
APAP*AT>1500	0.004	1.2	3.4	1.5 to 7.5
Nomogram band ≥150	0.002	1.0	2.7	1.4 to 5.2
Dose (mg)/kg ≥ 300	0.0001	1.4	3.8	2.3 to 6.5

F. INR peak >2 after delayed NAC treatment

Figure 3-8 shows the cumulative proportions of peak INR >2 vs time to NAC in SNAP and standard regimen. The incidence of those developing a peak INR >2 appeared to be higher in SNAP group. However, **Table 3-9** shows both regimens were comparable. The clinical characteristics of this group of patients is shown in **Table 3-17**. ALT level at admission and APAP× ALT products were significantly higher in SNAP group but there were no other significant differences between those treated with each of the two regimens.

In late presenters (more than 16h post-ingestion), the development of peak INR >2 with the SNAP regimen was not significantly different compared to the standard regimen (unadjusted OR 2.1, 95% CI 0.81 to 5.6, P=0.13). When other predictor variables were entered into the regression model, abnormal ALT at baseline, APAP× ALT >1500, and nomogram band >150 were significant predictors for INR peak > 2 in late presenters (**Table 3-18**).

In patients treated within 16h post-ingestion (**Table 3-19**), the occurrence of peak INR >2 demonstrated no statistical difference in SNAP group compared to the standard regimen (adjusted OR 1.3, 95% CI 0.63 to 2.76, P= 0.45).

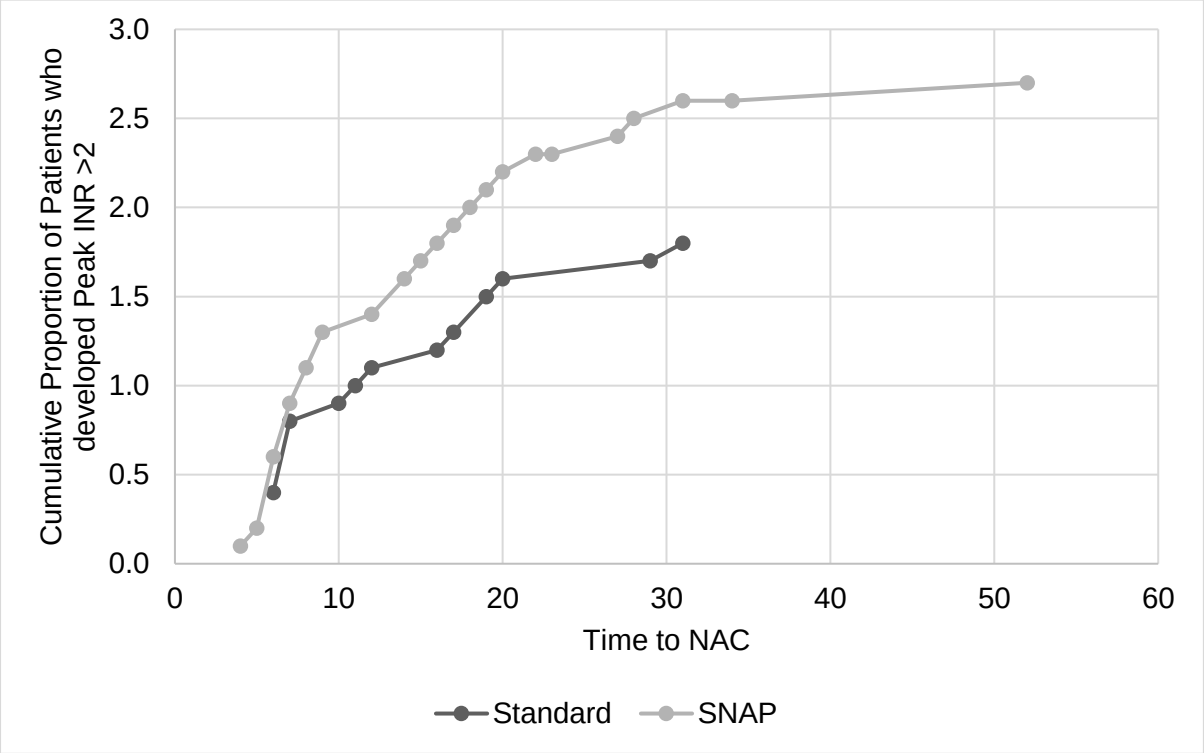


Figure 3-8: Cumulative proportion of patients with acute single overdose who develop peak INR>2 with each NAC regimen

Table 3-17: Demographic data of INR peak >2 patients with time to NAC >16 hours of acute single overdose

Factors	SNAP			Standard			SNAP Total (170)	Standard Total (129)	Absolute Difference % (95%CI)	P-value
	Newcastle 94	London 15	Edinburgh 61	Newcastle 28	London 6	Edinburgh 95				
Gender Male (%) Female (%)	38/94 (40.4) 56/94 (59.6)	10/15 (66.7) 5/15 (33.3)	22/61 (36.1) 39/61(63.9)	12/28 (42.9) 16/28 (57.1)	3/6 (50) 3/6 (50)	27/95(28.4) 68/95 (71.6)	70/170 (41.2) 100/170(58.8)	42/129 (32.6) 87/129 (67.4)	8.6 (-2.5 to 19.2)	P=0.13
Age year [median,(IQR)]	31 (27)	35 (30)	33.5 (33)	37 (32)	29 (46)	23.5 (24)	32(28)	28 (28)	Not applicable	P=0.18
Weight (KG) [median,(IQR)]	70 (25)	74 (28)	65.5 (28)	65 (24)	57.8 (22)	70 (21)	70 (25)	68 (23)	Not applicable	P= 0.64
Paracetamol dose/kg [median,(IQR)]	222 (195.5)	226 (360)	226 (216.5)	244 (229)	226 (333)	201.3 (165.3)	223 (209.3)	224.9 (193.9)	Not applicable	P=0.6
ALT admission [median,(IQR)]	32 (122)	27.5 (26)	26 (113)	33(76)	16.5 (3)	21 (31)	28 (95)	22 (40)	Not applicable	P=0.044
ALT admission Normal No. (%) Abnormal No. (%)	58/94 (61.7) 36/94 (38.3)	9/13 (69.29) 4/13 (30.8)	38/61 (62.3) 23/61 (37.7)	17/28 (60.7) 11/28 (39.3)	5/6 (83.3) 1/6 (16.7)	73/95 (76.8) 22/95 (23.2)	105/168 (62.5) 63/168 (37.5)	95/129 (73.6) 34/129 (26.4)	11.1 (-0.3 to 21.3)	P=0.04
INR admission [median,(IQR)]	1.1 (0.3)	1.0 (0.1)	1.1 (0.2)	1 (0.2)	1 (0.2)	1 (0.1)	1.1 (0.2)	1 (0.1)	Not applicable	P= 0.6
Extrapolated paracetamol at 4 h [median,(IQR)]	305.7 (1874)	149.2 (434)	N/A	130.8 (893)	234.8 (5792)	N/A	276.8 (1594.5)	141.6 (846.4)	Not applicable	P=0.24
Paracetamol× ALT products ≤1500 No. (%) >1500 No. (%)	64/93 (68.8) 29/93 (32.1)	9/12 (75) 3/12 (25)	42/60 (70) 18/60 (30)	19/28 (67.9) 9/28 (32.1)	6/6 (100) 0/6 (0)	72/93 (77.4) 21/93 (22.6)	115/165 (69.7) 150/165 (30.3)	97/127 (82.9) 30/127 (17.1)	13.2 (3.3 to 22.5)	P=0.01
Time to NAC (h) [median,(IQR)]	22 (14)	20.5 (7)	21.9 (7)	23(9)	22 (15)	22.5 (9)	22 (9)	23 (9)	Not applicable	P=0.84
Nomogram Band (%) <150 ≥ 150	31/93 (33.3) 62/93 (66.7)	6/13 (46.2) 7/13 (53.8)	29/61 (47.5) 32/61 (52.5)	15/27 (55.6) 12/27 (44.4)	3/6 (50) 3/6(50)	29/68 (42.6) 39/68 (57.4)	66/167 (39.5) 101/167 (60.5)	47/101 (46.5) 54/101 (53.5)	7 (- 5.1 to 18)	P=0.26

Table 3-18: Binary logistic regression of INR peak >2 in patients with acute single overdose treated with NAC >16h post-ingestion

Time to NAC >16	Outcome: INR peak >2			
Univariate regression analysis	**P=**	**B**	**odds**	**95% C.I for odds**
Regimen (SNAP)	0.129	0.76	2.1	0.81 to 5.6
Abnormal ALT at baseline	0.0001	4.0	54.98	7.3 to 415.9
Time to NAC	0.38	-0.02	0.98	0.94 to 1.02
APAP*AT>1500	0.0001	3.6	35.0	7.9 to 153.9
Nomogram band ≥150	0.046	1.1	3.14	1.02 to 9.65
Dose (mg)/kg ≥ 300	0.0001	2.1	8.16	2.9 to 23.1
Age (Year) >30	0.24	0.54	1.7	1.12 to 6.26
Patient Wt. (kg)	0.26	-0.13	0.987	0.96 to 4.2
Multivariate regression analysis				
Regimen (SNAP)	0.75	0.21	1.2	0.33 to 4.7
Abnormal ALT at baseline	0.03	2.5	12.4	1.4 to 112.6
APAP*AT>1500	0.006	2.6	13.7	2.1 to 88.9
Nomogram band ≥150	0.023	-1.03	0.36	0.07 to 1.9
Dose (mg)/kg ≥ 300	0.19	0.86	2.4	0.65 to 8.6

Table 3-19: Binary logistic regression of INR peak >2 in patients with acute single overdose treated with NAC ≤16h post-ingestion

Time to NAC ≤16	Outcome INR peak >2			
Univariate regression analysis	**P=**	**B**	**odds**	**95% C.I for odds**
Regimen (SNAP)	0.29	0.34	1.4	0.74 to 2.8
Abnormal ALT at baseline	0.0001	1.6	5.1	2.7 to 9.5
Time to NAC	0.02	0.11	1.1	1.01 to 1.2
APAP*AT>1500	0.005	2.9	17.7	2.4 to 129.1
Nomogram band ≥150	0.0001	2.2	8.7	3.1 to 24.6
Dose (mg)/kg ≥ 300	0.0001	1.5	4.3	2.2 to 8.4
Age (Year) >30	0.14	0.46	1.6	0.86 to 2.95
Patient Wt. (kg)	0.39	-0.008	0.99	0.98 to 1.01
Multivariate regression analysis				
Regimen (SNAP)	0.45	0.28	1.31	0.63 to 2.76
Abnormal ALT at baseline	0.001	1.3	3.6	1.7 to 7.56
Time to NAC	0.003	0.17	1.2	1.1 to 1.3
APAP*AT>1500	0.046	2.1	8.2	1.04 to 65.2
Nomogram band ≥150	0.01	1.4	3.9	1.3 to 11.8
Dose (mg)/kg ≥ 300	0.02	0.9	2.4	1.2 to 4.99

G. Peak ALT>1000 compared to historical studies

1. Nomogram band

Table 3-20 provides a comparison of the proportion of patients who developed ALT peak >1000 in our current study compared to historical cohorts of patients. In comparison with data from previous studies, there was no evidence of the SNAP regimen being inferior in patients taking large acute single paracetamol overdoses.

Table 3-20: Historical studies in patients with large paracetamol overdoses treated with standard regimen showing proportion developing hepatotoxicity based on nomogram band categorization.

Reference	Nomogram band				
	<150	150-299	≥300	**Unknown**	**Total**
1. SNAP					
a. (Current study)	7/844 (0.8)	27/691 (3.9)	20/137 (14.6)	3/105 (2.9)	57/1777 (3.2)
2. Standard regimen					
a. Current standard	2/431 (0.5)	16/499 (3.2)	6/42 (14.3)	6/168 (3.6)	30/1140 (2.6)
b. Sivilotti (CAOS), 2005 (153)	0/404 (0)	14/528 (2.7)	80/338 (23.7)	0(0)	94/1270 (7.4)
c. Cairney, 2016 (103)	7/ 265 (2.6)	10/335 (3)	13/127 (10.2)	0(0)	30/727 (4.1)
d. Greene, 2016(154)	0/179 (0)	3/238(1.2)	17/112 (15.2)	0(0)	20/529 (3.8)
e. Chiew, 2017 (121)	n/a	n/a	n/a	n/a	28/200 (14)
f. Chiew, 2018 (155)	n/a	n/a	n/a	n/a	21/113 (18.6)

We analysed in more detail the data in Newcastle and London of 137 patients who were treated within 24h of ingestion with the SNAP regimen and had paracetamol concentrations above the 300 nomogram-line.

83/137(60.6%) patients (median weight 75kg) reported a median ingested paracetamol dose of 28.8g and were treated with the 12h 2-bag SNAP regimen only and did not develop acute liver injury at least 24h post-ingestion.

54/137(39.4%) patients (mean weight 70kg) reported a mean ingested paracetamol dose of 37g and required extended NAC treatment. 34/137 (24.8%) developed acute liver injury (peak ALT>100 IU/L). Hepatotoxicity (peak ALT>1000 IU/L) developed in 20/137 (14.6%) patients, including 3/44 treated within 8h post-ingestion, 4/45 treated within 8-16h and 13/48 treated within 16-24h. 19/20 patients who developed hepatotoxicity had evidence of acute liver injury (ALT>10 IU/L) and the other patient had a paracetamol concentration of 71mg/L at the end of the 12h infusion. There were no deaths or liver transplants. Compared to a historical UK cohort of 112 patients with acute single paracetamol overdose above the 300-nomogram line treated with the conventional 21h NAC regimen(154), development of acute liver injury (24.8% vs 33%, difference -8.2%, 95% CI: -3.02% to 19.4%, p=0.15), and hepatotoxicity (14.6 % vs 15.2%, difference -0.6%, 95% CI: -8.2% to 9.8%, p=0.89) was not statistically different with the SNAP regimen.

2.Time to start NAC

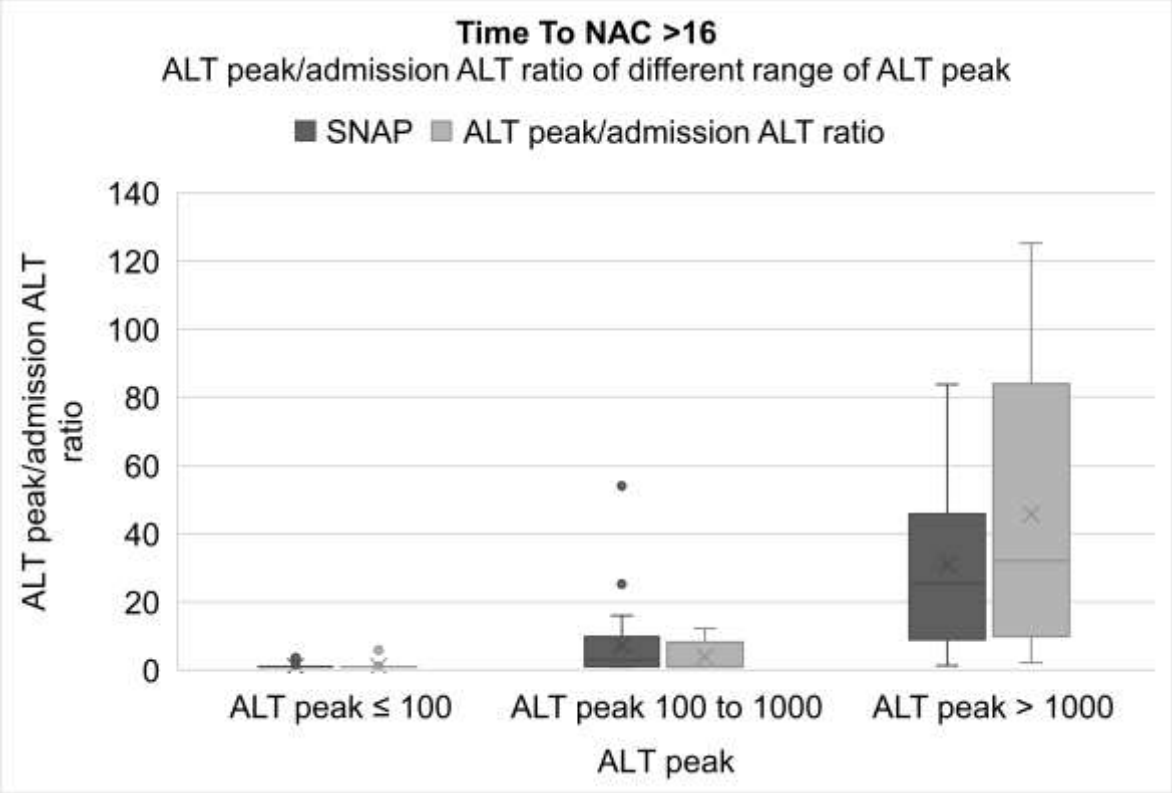
Table 3-21 shows the proportion of ALT >1000 in patients who received NAC >16 h post overdose in our current study compared to the historical cohort. The data indicated that the development of hepatotoxicity in group of patients who had NAC 16 hours or more post ingestion our current standard regimen was extremely low compared to the published studies

Table 3-21: Historical studies in patients with large paracetamol overdoses treated with standard regimen showing proportion developing hepatotoxicity based on time to start NAC

Reference	Time to Start NAC			
	< 16	≥ 16	**Unknown**	**Total**
SNAP				
(Current study)	34/1495(2.3)	21/162(13)	2/120(1.7)	57/1777(3.2)
Standard regimen				
Current standard	17/860 (2)	6/125 (4.8)	7/155 (4.5)	30/1140 (2.6)
Sivilotti (CAOS), 2005	53/974 (5.4)	40/149(26.8)	1/147(0.7)	94/1270 (7.4)
Chiew, 2017	15/174(8.6)	13/26 (50)	0(0)	28/200 (14)

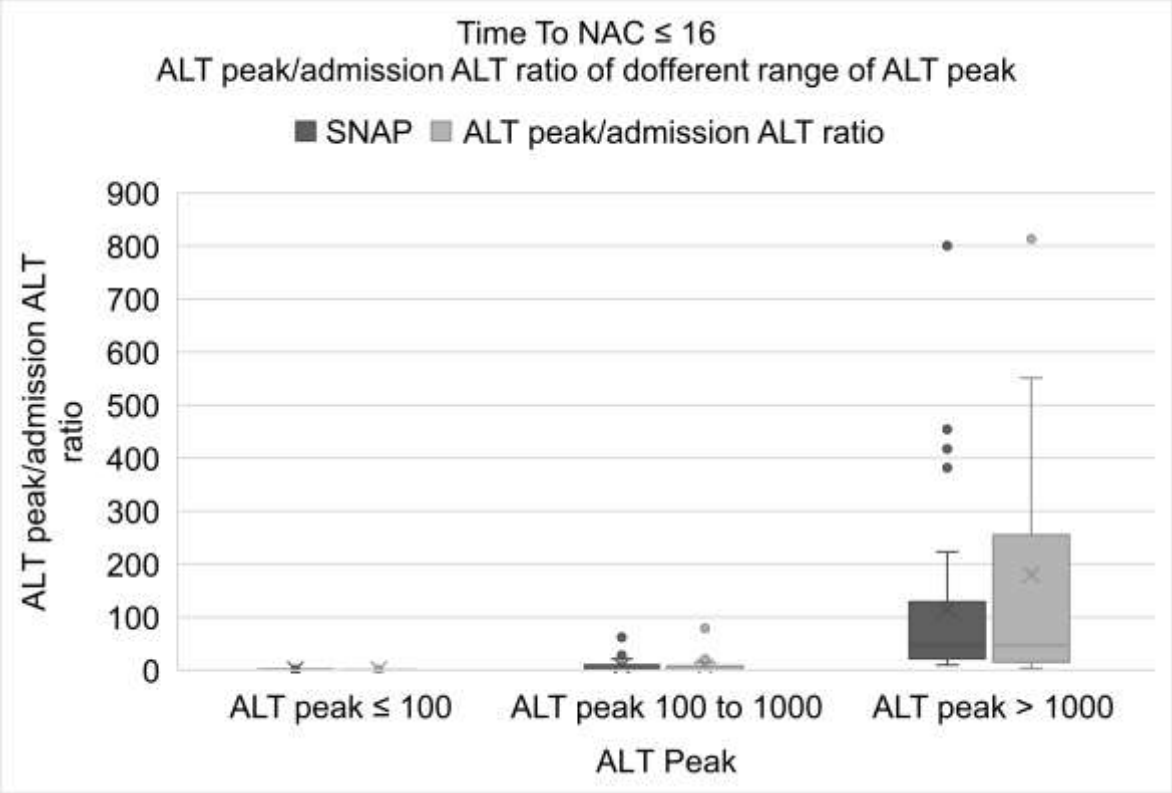
H. Peak ALT/admission ALT ratio

An abnormal ALT at baseline is a strong predictor of peak >1000 and INR peak >2. ALT peak/admission ALT ratio was calculated for all patients to evaluate whether there are differences in the degree of hepatocellular injury between patients treated with the SNAP and standard regimens in patients with time to NAC >16 h and ≤ 16h The peak ALT/admission ratio was compared between 3 groups: ALT peak <100, 100 to 1000, and >1000. The median peak ALT/admission ALT ratio was not significantly different between the two regimens both patients treated more than 16h **(Figure 3-9**) and within 16h (**Figure 3-10**).



Median	ALT peak ≤ 100	ALT peak 100 to 1000	ALT peak > 1000
SNAP	1	3.06	25.44
Standard	1	1.03	32.05
P value	0.423	0.139	0.67

Figure 3-9:ALT peak /admission ALT ratio in patients with late presenter of acute single overdose

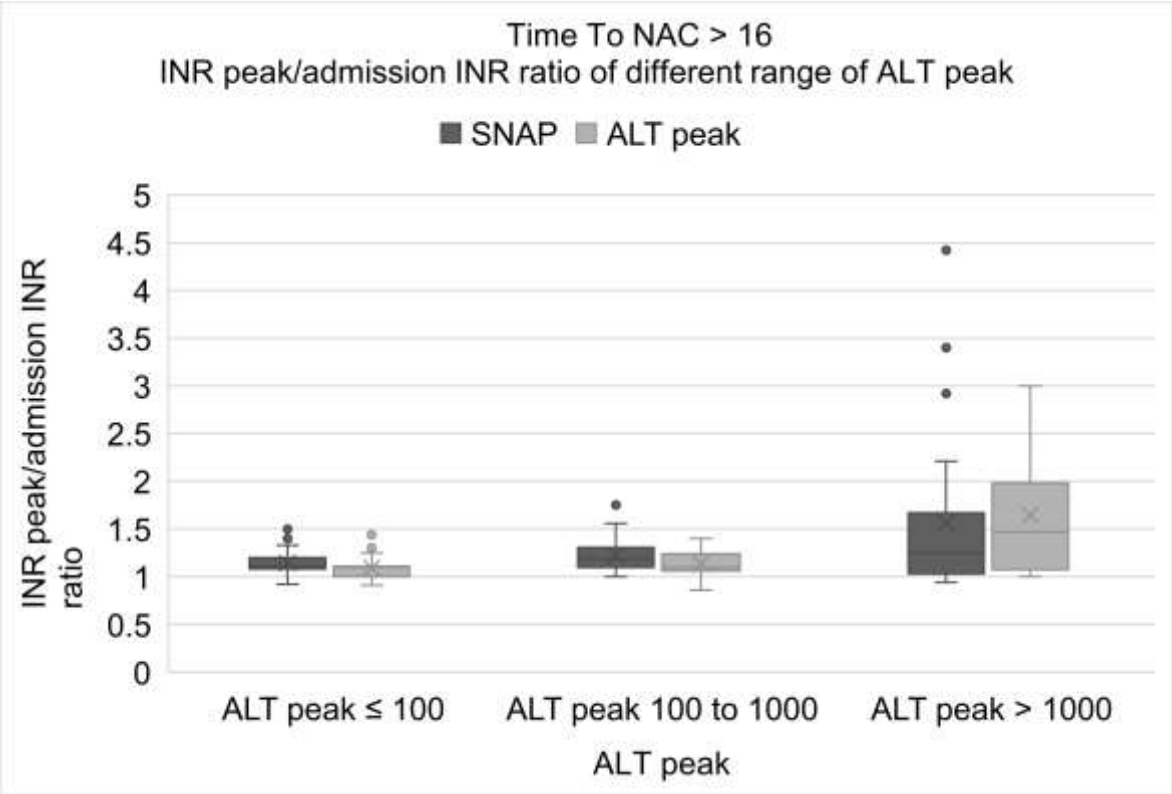


Median	ALT peak ≤ 100	ALT peak 100 to 1000	ALT peak > 1000
SNAP	1	2.7	46.4
Standard	1	1.005	47
P value	0.022	0.182	0.767

Figure 3-10: ALT peak /admission ALT ratio in patients with time to NAC ≤ 16 of acute single overdose

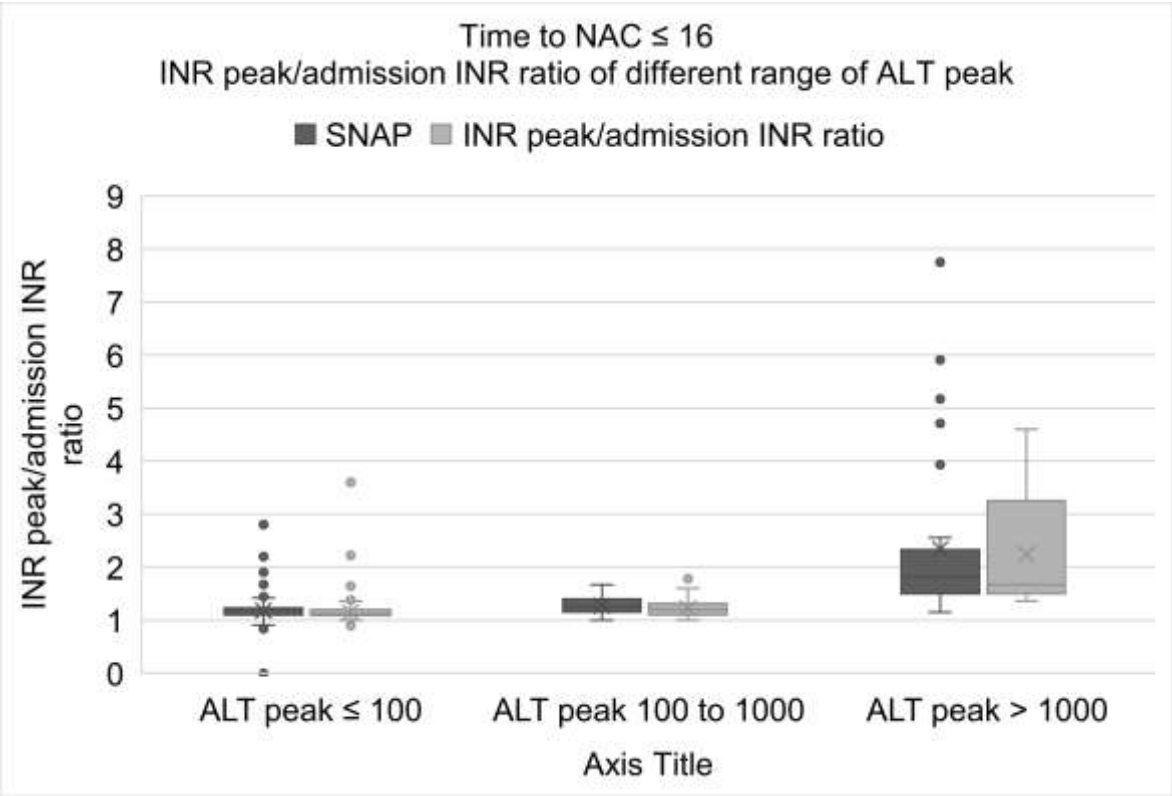
I. Peak INR/admission INR ratio

Peak INR >2 is strong predictor of hepatotoxicity. INR peak/admission INR ratio was calculated for all patients to evaluate whether its impact on the outcomes in patients treated with the SNAP and standard regimens. The data was based on time to NAC (>16 h and ≤ 16h). The peak INR/admission ratio was compared between 3 groups: ALT peak <100, 100 to 1000, and >1000. The median peak INR/admission ALT ratio was not significantly different between the two regimens both patients treated more than 16h (**Figure** 3-11) and within 16h (**Figure** 3-12).



Median	ALT peak ≤ 100	ALT peak 100 to 1000	ALT peak > 1000
SNAP	1.11	1.19	1.25
Standard	1.1	1.1	1.47
P value	0.2	0.15	0.7

Figure 3-11: INR peak /admission INR ratio in patients with time to NAC >16h of acute single overdose.



Median	ALT peak ≤ 100	ALT peak 100 to 1000	ALT peak > 1000
SNAP	1.2	1.25	1.82
Standard	1.11	1.2	1.67
P value	0.1	0.07	0.87

Figure 3-12:INR peak /admission INR ratio in patients with time to NAC ≤ 16h of acute single overdose.

3.3.2. Staggered Overdose:

There were no significant differences in the baseline characteristics of patients taking staggered overdoses with the SNAP and standard regimen except for abnormal ALT (>50 IU/L) on admission which was statistically significantly more common in those treated with the standard regimen (**Table 3-22**). There was no difference in the proportion of patients developing ALT >1000 between the two regimens overall but patients treated with the SNAP regimen had fewer NAARs requiring antihistamine treatment (**Table 3-23**). In the Edinburgh cohort, hepatotoxicity was significant lower in the SNAP group (0.7% vs 3.4, 95% CI 0.13 to 6.57, P=0.03).

Table 3-22: Demographic data of patients with staggered overdose

Staggered Overdose Factors	SNAP			Standard			Total per regimen [N (%)]		Absolute Difference % (95%CI)	P-value
	Newcastle 361	London 104	Edinburgh 290	Newcastle 78	London 77	Edinburgh 176	**SNAP (755)**	**Standard (331)**		
Gender Male No. (%) Female No. (%)	144/361 (39.9) 217/361 (60.1)	49/104(47.1) 55/104(52.9)	65/290 (22.4) 225/290 (77.6)	36/78 (46.2) 42/78 (53.8)	45/76 (40.3) 31/76 (58.4)	124/176 (29.5) 52/176 (70.5)	258/755 (34.2) 497/755 (65.8	119/330 (36.1) 211/330 (63.9)	1.9 (- 4.2 to 8.2)	P=0.54
Age year [median,(IQR)]	31 (22)	31 (22)	38(17)	33(27)	32(20)	35.5(19)	32(20)	34.5(21)	No applicable	P=0.79
Wight (KG) [median,(IQR)]	75 (25)	72 (25)	80 (37)	68(24)	70 (30)	75 (27)	75 (30)	74 (25)	No applicable	P =0.89
Paracetamol dose/kg [median,(IQR)]	207.3 (192.5)	203.4(211.3)	166 (127)	226.2(241.5)	244.8 (145.7)	170.6 (140.2)	187 (162.6)	181.8 (147.2)	No applicable	P =0.74
ALT admission [median,(IQR)]	21 (20)	20 (17)	20 (16)	24 (32)	22 (26)	20 (22)	21 (17)	21 (25)	No applicable	P =0.25
ALT admission Normal No. (%) Abnormal No. (%)	298/354 (84.2) 56/354 (15.8)	84/93 (90.3) 9/93 (9.7)	250/289 (86.5) 39/289 (13.5)	61/76 (80.3) 15/76 (19.7)	24/28 (85.7) 4/28 (14.3)	139/175 (79.4) 36/175 (20.6)	632/736 (85.9) 104/736 (14.1)	224/279 (80.3) 55/279 (19.7)	5.6 (0.57 to 11.2)	P=0.028
INR admission [median,(IQR)]	1 (0.1)	1 (0.2)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.2)	1 (0.1)	1 (0.2)	No applicable	P =0.59
Paracetamol× ALT products ≤1500 No. (%) >1500 No. (%)	244/348 (70.1) 104/348 (29.9)	64/87 (73.6) 23/87 (26.4)	200/289 (69.2) 89/289 (30.8)	45/74 (60.8) 29/74 (39.2)	14/24(58.3) 10/24 (41.7)	112/175 (64) 63/175 (36)	508/724 (70.2) 63/724 (29.8)	171/273 (62.2) 102/273 (37.4)	8 (1.5 to 14.7)	P= 0.015

Table 3-23: ALT peak >1000IU/l in patients with staggered overdose

Staggered Overdose Location/Regimen	SNAP [N (%)]			Conventional [N (%)]			Total per regimen [N (%)]		**Absolute Difference % (95%CI)**
	Newcastle	London	Edinburgh	Newcastle	London	Edinburgh	SNAP	Conventional	
	361	104	290	78	77	176	755	331	
ALT Peak >1000	8/361 **(2.2)**	2/104 **(1.9)**	2/289 **(0.7)**	4/78 **(5.1)**	1/75 **(1.3)**	6/175 **(3.4)**	12/754 **(1.6)**	11/328 **(3.4)**	-1.8 (-0.1 to 4.5)
NAARs Yes (%) No (%)	0/354 (0) 354/354 (100)	3/93 (3.2) 90/93 (96.8)	N/A	6/76 (7.9) 70/76 (92.1)	4/28(14.3) 24/28 (85.7)	N/A	3/447 (0.7) 444/447 (99.3)	10/104 (9.6) 94/104 (90.4)	8.9 (4.4 to 16.1) P=0.0001

3.3.3. Therapeutic Excess

The clinical characteristics of patients with chronic therapeutic excess paracetamol treated with the SNAP and standard regimen are shown in **Table 3-24**. There were no differences between the two groups, but patients treated with the standard regimen had a significantly higher rate of NAARs. There was no difference in development of ALT peak >1000 IU/l progression between SNAP and standard groups (**Table 3-25**) in all of the 3 centres.

Table 3-24: Demographic data of patients with therapeutic excess

Factors Therapeutic Excess	SNAP			Standard			Total per regimen [N (%)]		Absolute Difference % (95%CI)	P-value
	Newcastle 100	London 89	Edinburgh 170	Newcastle 48	London 70	Edinburgh 168	**SNAP (359)**	**Standard (286)**		
Gender Male No. (%) Female No. (%)	41/100 (41) 59/100 (59)	36/89(40.4) 53/89 (59.6)	69/170 (40.6) 101/170 (59.4)	13/48 (27.1) 35/48 (72.9)	40/70 (57.1) 29/70 (41.4)	81/168 (48.2) 87/168 (51.8)	146/359 (34.2) 213/359 (65.8	134/286 (36.1) 151/286 (63.9)	1.9 (- 5.5 to 9.3)	P=0.25
Age year [median,(IQR)]	33.5 (22)	34 (23)	35.5(20)	26(11)	27(25)	31(24)	34(22)	31(22)	No applicable	P=0.51
Wight (KG) [median,(IQR)]	71 (27)	72 (28)	75 (25)	72(26)	70.6 (22)	68 (18)	73 (26)	69 (18)	No applicable	P =0.16
Paracetamol dose/kg [median,(IQR)]	170.5 (152.4)	139.5 (137.2)	123 (72)	207.9 (246.1)	112 (51.4)	125 (84.1)	138.5 (91.5)	127.3 (105)	No applicable	P =0.11
ALT admission [median,(IQR)]	22 (25)	22 (23)	24 (34)	15 (17)	32.5 (30)	24 (28)	22 (25)	23 (29)	No applicable	P =0.89
ALT admission Normal No. (%) Abnormal No. (%)	74/97 (76.3) 23/97 (23.7)	58/75 (77.3) 17/75 (22.7)	119/165 (72.1) 46/165 (27.9)	38/47 (80.9) 9/47 (19.1)	11/15 (73.3) 4/15 (26.7)	122/167 (73.1) 45/167 (26.9)	251/337 (74.5) 86/337 (25.5)	171/229 (74.7) 58/229 (25.3)	0.2 (- 7.2 to 7.3)	P=0.95
INR admission [median,(IQR)]	1 (0.1)	1 (0.2)	1 (0.1)	1 (0.1)	1 (0)	1 (0.1)	1 (0.1)	1 (0.1)	No applicable	P =0.11
Paracetamol× ALT products ≤1500 No. (%) >1500 No. (%)	82/92 (89.1) 10/92 (10.9)	60/66 (90.9) 6/66 (9.1)	142/163 (87.1) 21/163 (12.9)	44/45 (97.8) 1/45 (2.2)	104/11(90.9) 1/11 (9.1)	150/166 (90.4) 16/166 (9.6)	284/321 (88.5) 37/321 (11.5)	204/222 (91.9) 18/222 (8.1)	3.4 (-1.9 to 8.3)	P= 0.2

Table 3-25: ALT peak >1000IU/l in patients with therapeutic excess

Chronic Overdose Location/Regimen	**SNAP [N (%)]**			**Conventional [N (%)]**			**Total per regimen [N (%)]**		**Absolute Difference % (95%CI)**
	Newcastle	London	Edinburgh	Newcastle	London	Edinburgh	SNAP	Conventional	
	100	89	170	48	70	168	359	286	
ALT Peak >1000	0/100 **(0)**	1/88 **(1.1)**	1/168 **(0.6)**	1/48 **(2.1)**	1/69 **(0)**	2/165 **(1.2)**	1/356 **(0.6)**	3/284 **(1.1)**	0.5 (-1.1 to 2.6)
NAARs Yes (%) No (%)	4/97 (4.1) 93/97 (95.9)	2/75 (2.7) 73/75 (97.3)	N/A	7/47 (14.9) 40/47 (85.1)	3/15(20) 12/15 (80)	N/A	6/172 (3.5) 166/172 (96.5)	10/62 (16.1) 52/62 (83.9)	12.6 (4.5 to 23.8) P=0.0008

3.4. Discussion:

Intravenous NAC is considered the drug of choice for prevention of acute hepatic injury following paracetamol overdose in the UK and many other countries. A 21h 3-bag standard NAC regimen has been recommended in the UK since September 2012. The SNAP study showed that a slower initial infusion rate of NAC caused fewer adverse effects, and this justified the implementation of a modified 2-bag 12h acetylcysteine (NAC) regimen ('SNAP') into routine clinical practice in three UK hospitals. It was also simpler and quicker to administer than the standard 3-bag 21h NAC regimen. However the efficacy of the SNAP regimen is uncertain in high-risk patients such as late presenters or those with large overdoses (152, 156, 157) as previous studies were not sufficiently powered to confirm efficacy in these sub-groups (96, 134). This observational study, involving a large cohort of patients, was undertaken to assess the efficacy of the SNAP regimen in preventing acute liver injury and hepatotoxicity compared to the standard regimen in patients with paracetamol overdose, taking into account factors that may influence the outcome.

There was no significant difference in the primary outcome (development of peak ALT >1000) between the SNAP regimen and standard regimen in acute single overdose, staggered overdose, and therapeutic excess of paracetamol. These results are consistent with previous studies(134), (96). The SNAP regimen also appeared less effective in patients treated more than 16 hours post-ingestion, but when adjusted for confounding factors, this difference was no longer statistically significant (adjusted odds ratio 1.31, 95%CI: 0.31 to 5.16, P=0.67). A possible explanation for this is that a lower proportion of high-risk patients were treated with the standard regimen as a result of the retrospective nature of data collection which may have led to a bias towards patients remaining in the acute medical unit and exclusion of patients transferred to critical care or a liver unit. This is reflected in the very low proportion developing the primary outcome of ALT>1000 in the late presenters treated compared to historical cohorts. On the other hand, the data for the SNAP regimen was collected systematically in a prospective manner which ensured all patients data were included. The current findings are also in keeping with studies undertaken with the Australian two-bag NAC regimen, (200 mg/kg over 4 h, 100 mg/kg over 16 h) in high risk group of patients which showed that the incidence of hepatotoxicity in patients treated 8 to

24 h and more than 24 h were 1.2% vs 1.6%, 95% CI -1.75 to 0.91 and 14% vs 16% , 95% CI -12 to 8.3 with the two-bag and three-bag regimens, respectively(158).

Our study also shows that the main predictors of hepatotoxicity in patients treated with NAC were elevated ALT on admission, APAP×AT product >1500 mg/l × IU/l , nomogram band greater than 150, and large overdose ≥300mg/kg. The accuracy of APAP×AT products to predict hepatotoxicity in acute single overdose patients was estimated in 410 patients by Wong et al. The pre-specified cut off value of APAPxAT product 1500 mg L^{-1}× IU L^{-} h was highly predictive of developing ALT peak >1000 IU/l (sensitivity and specificity of 100% and 92%, respectively)(145). This parameter is particularly useful in patients who present more than 16h post-ingestion, when the paracetamol concentration is often very low and makes risk stratification difficult.

In patients taking very large overdoses, despite NAC treatment within 8 hours of overdose, paracetamol concentration above the 300-nomogram line and massive overdose ingestion (>250mg/kg) have been shown to be associated with a significantly increased risk of hepatotoxicity (adjusted OR: 1.46, 95% CI: 1.15 to 1.86, p = 0.002 and 2.13, 95% CI: 1.32 to 3.45, p = 0.002, respectively) (154).

Similarly, we found in this cohort of patients that doses >300mg/kg and nomogram band >300 were important predictors of hepatotoxicity. Although the numbers involved were relatively small, patients with concentrations above the 300-line who were treated with the SNAP regimen did not appear to do worse than those treated with the standard regimen either in this cohort or in historical cohorts. This study therefore alleviates the concern raised by Harmouche and colleagues who opposed use of the two-bag regimen with a lower initial dose as the evidence about safety and efficacy of the two-bag regimen was previously based on a low-risk group of patients.

The next outcome is INR more than 2 following treatment with either SNAP or the standard protocol. Although it is known that treatment with NAC has a dose-dependent effect on INR, there was no significant difference in the risk of developing INR peak> 2 between the SNAP and standard regimen (OR 1.38, 95% CI: 0.7 to 2.5, P= 0.38). It is interesting to note that there was also no difference in the sub-group of late presenters who are at higher risk of developing hepatic synthetic dysfunction.

The risk of hepatotoxicity in patients with chronic therapeutic excess was very low and no different between the 2 regimens, reflecting the treatment of low-risk patients in the

UK during the period of the study. A systematic review found that having both a normal ALT and a low paracetamol concentration <20mg/l at presentation was associated with an extremely low risk of acute liver injury in patients with chronic therapeutic excess and treatment guidelines now advise that patients who have a normal ALT and undetectable paracetamol at least 4 hours since their last ingestion do not require treatment with NAC (154, 159). In Australia, an 8-hour NAC protocol has been suggested for routine use in patients with repeated supratherapeutic ingestions (RSTI) of paracetamol (138).

This study also confirms the significantly lower rate of NAARs with the SNAP regimen compared to the standard regimen in all patterns of overdose. These results support the previous results of a randomised controlled study showing that grade 3 severe reactions that need either treatment or infusion interruption were 5/108 (4.6%) and 31/100 (31%) after use of the SNAP or standard protocols, respectively (96).

The safety profile and simplicity of the SNAP regimen justifies its use in clinical practice. This study provides additional evidence of clinical effectiveness, justifying use of the SNAP regimen as the standard of care in UK hospitals.

Study Limitations

This an observational study and as such subject to biases from unmeasured confounding. Although the results appear to confirm the effectiveness of the SNAP regimen in most patient groups, it is not possible to state categorically that this may not be differences in high-risk subsets of patients where small patient numbers have been studied.

There have been changes in the type of patient medical records used in the UK healthcare system during this time period with a shift from paper records to digitisation and electronic medical records. For example, in Newcastle, digitisation started in 2013 and took around five years (from 2014 to 2019) to transform and to create a single electronic care record for patients and provide a single Information Technology (IT) platform for health professionals. As a result, it is possible that a number of patients who were treated with the standard regimen were not captured during data collection. This could have generated less accurate results for 21h standard regimen. As the timeline for digitisation was different in the 3 hospitals, there may be some variation in completeness of data between centres.

CHAPTER 4

IMPACT OF THE SNAP REGIMEN ON THE INTERNATIONAL NORMALIZED RATIO (INR)

Chapter 4 Impact of a 12 h SNAP Acetylcysteine (NAC) regimen on the International Normalized Ratio (INR)

4.1. Introduction

NAC is the principal treatment for patients with paracetamol overdose to reduce the risk of developing hepatotoxicity and fulminant hepatic failure and is most effective when treatment starts within 8 hours of ingestion in most patients (30). At the end of treatment with NAC, transaminases and prothrombin time are used as laboratory indicators of the effectiveness of NAC in preventing hepatic injury in those patients. However, it has been observed that isolated minor prolongation in prothrombin time can occur without evidence of hepatotoxicity in patients with paracetamol overdose as well as those treated with NAC (160).

It has been established that paracetamol can interfere with the coagulation cascade, and isolated elevation of the prothrombin time without evidence of hepatotoxicity is well recognized with paracetamol ingestion (161). Paracetamol can inhibit vitamin-K-dependent coagulation factors especially factor VII (short half-life), by inhibition of γ-glutamyl carboxylase, which activates coagulation factors II, VII, IX, and X(162). Clinically, it was found that 50% of patients with paracetamol overdose at the time of presentation had an INR > 1.26 even if the aminotransferase enzyme was normal (163). This was attributed to paracetamol reducing the functional effect of vitamin K-dependent clotting factors rather than directly inhibiting synthetic liver function.(Whyte et al, 2000) Furthermore, in a systematic review, paracetamol dose was shown to be significantly correlated to the INR with an average increase in INR of 0.17 per gram of paracetamol ingested (95% CI: 0.004 to 0.33) (164). Therefore, paracetamol itself can increase prothrombin time despite normal hepatic function and this needs to be taken in consideration in the management of patients with paracetamol toxicity.

As well as paracetamol, NAC also interferes with coagulation(165), depressing significantly coagulation factors II, VII, and X following administration of a therapeutic dose in healthy subjects. The anticoagulant activity of NAC is reversible and most likely due to the reduction of disulphide bonds of these clotting factors, resulting in inactivation of their catalytic role(160), which is essential to maintain their biological activity.

An elevation of prothrombin time has been reported in 87 patients who had paracetamol poisoning without evidence of hepatic injury (166). The study found that NAC can increase the INR from 1·03 to 1·28 during the first 8 hours of the NAC infusion. The authors used multivariate analysis and demonstrated that the fall in coagulation activity was strongly associated with NAC therapy rather than paracetamol ingestion. The impact of the standard NAC protocol for management of paracetamol overdose (150 mg/kg in 200 ml over 15 min, followed by 50 mg/kg over 4 h and 100 mg/kg over 16 h)(160) was evaluated in 18 patients who developed an isolated elevation in INR with normal liver profile at the end of NAC infusion. The study found the maximum increase of 21% in prothrombin time was at 14 h post NAC treatment, although the prothrombin time in those patients was normal at baseline and at an average 8.6 h post paracetamol ingestion.

The effect of NAC on prothrombin time was measured in healthy volunteers using four different concentrations of NAC(167). The mean prothrombin time was 13.9, 14.2, 15.5, and 17.4 at plasma NAC concentrations of 0 (control), 250, 500, and 1000 mg/l respectively, confirming a dose-dependent effect of NAC in prolonging prothrombin time.

While prothrombin time increases in patients with paracetamol overdose without indication of liver failure, this could lead to an unnecessary decision to continue treatment when risk of hepatotoxicity is very low (166). Current UK guidelines recommend continuing NAC in patients with INR>1.3 at the end of treatment(26), irrespective of the presence of hepatic injury, while Australian and New Zealand guidelines base their decision to continue treatment on ALT alone.

Moreover, a modified 12 h SNAP regimen includes a maintenance infusion of 200 mg/kg over 10 h (20 mg/kg/h) and this achieves higher steady-state NAC concentrations than with the standard regimen. This may have an impact on the INR due to the dose-dependent effect of NAC on INR. It is therefore important to assess the effect of NAC on INR in a cohort of patients hospitalized for paracetamol overdose who have a normal liver profile and who were treated with the 12 h SNAP regimen.

Objectives:

- To measure the effect of NAC on INR in patients with a normal liver profile treated with SNAP regimen.
- To measure the impact of stopping the NAC infusion on INR in patients with isolated INR elevation and normal liver profile.

4.2. Methodology

A modified 12 h (SNAP) regimen consisting of intravenous NAC 100 mg/kg over 2 h then 200 mg/kg over 10 h was introduced in 2016 in two teaching hospitals in UK for all patients who required NAC treatment for paracetamol poisoning. In this cohort of patients treated with the 12 h SNAP regimen, we evaluated the effect of NAC on the INR in patients with isolated INR elevation without evidence of liver injury at the end of 12h 'SNAP' regimen.

All patients who had an isolated INR >1.3 and alanine aminotransferase (ALT) < 40 U/l at the end of 12 h NAC infusion, at least two serial measurements of prothrombin time, and who completed the infusion either less than 24 hours or more than 24 hours post-paracetamol ingestion were included in the current study. All patients who were taking anticoagulant drugs were excluded from our study.

The change in INR was measured for the following time periods:

1) Admission (blood sample taken after patient admission and before NAC initiation) to 12 h after initiation of NAC treatment (blood sample at the end of 12 h NAC infusion).
2) 12 h to 24 h after initiation of NAC treatment (blood sample taken at 24 h post-ingestion after stopping NAC infusion if the infusion ended less than 24 hours post-paracetamol ingestion).

Data were analysed with the Statistical Package IBM SPSS 25. Differences were reported as statistically significant if the P value was less than 0.05. Data are expressed as frequencies and graphs using Excel 2016.

4.3. Results

1868 patients were admitted with a diagnosis of paracetamol overdose and treated with the SNAP regimen, but 5 patients taking anticoagulants and 55 patients with no blood tests at baseline were excluded from our analysis. Of the remaining 1808, 177

(9.8%,70% female) had an isolated INR elevation without evidence of liver injury at the end of the 12 h SNAP regimen (Figure 4-1). Of these, 77% had taken an acute single overdose and 20% a staggered overdose. The mean age was 29 years (range, 13-96), the median amount of paracetamol consumed was 209 mg/kg (range, 32-1818 mg/kg), and 68% (121 patients) reported ingesting more than 150 mg/kg paracetamol. There were 72 patients (40%) with an extrapolated 4-h paracetamol concentration greater than 150 mg/l (i.e above the 150-nomogram line) and 31 patients with chronic alcohol excess at the time of paracetamol overdose.

The median INR value at baseline was 1.1, which is measured at a median (IQR) time from paracetamol overdose of 7±(4) h. INR increased after NAC was initiated in 98.3% patients (174/177) from 1.2 to 1.4 with a median (IQR) change of 20 ± (13)%, range, -14% to 40% relative to baseline (P=0.0001) (**Table 4-1**Table 4-2). The median increase in INR from admission to the end of the12 h infusion was 0.3 (Range, -0.2 to 0.9) as shown in **Figure 4-2.**

Of the 177 patients, 34 received additional NAC treatment, 75 were discharged as they were more than 24 h post-ingestion, and 68 did not receive additional NAC and had a repeat blood sample taken at least 24 h post-ingestion (**Table 4-2**). None of the 75 patients who were discharged were readmitted within 7 days with acute liver injury. The change of INR in the 68 patients who did not receive additional NAC is shown in **Figure 4-3**. The INR was unchanged or fell in 66/68 from 1.4 to 1.3 within a median (IQR) time of 5.5 (4.6) h (P=0.0001, **Table 4-3**). In 2 patients, the INR rose from 1.4 to 1.5 but the ALT remained normal.

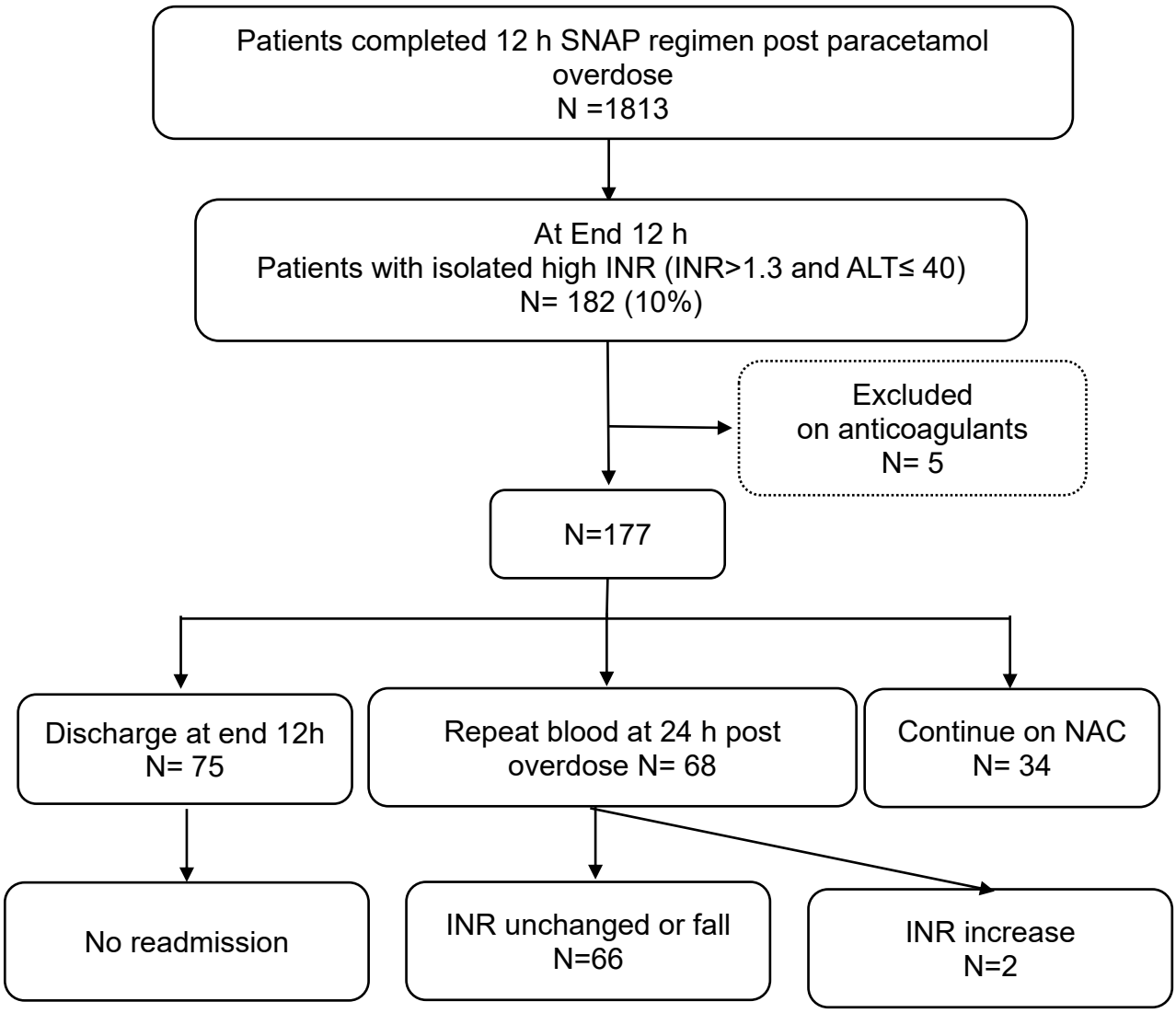


Figure 4-1: Flow diagram for study participants**.**

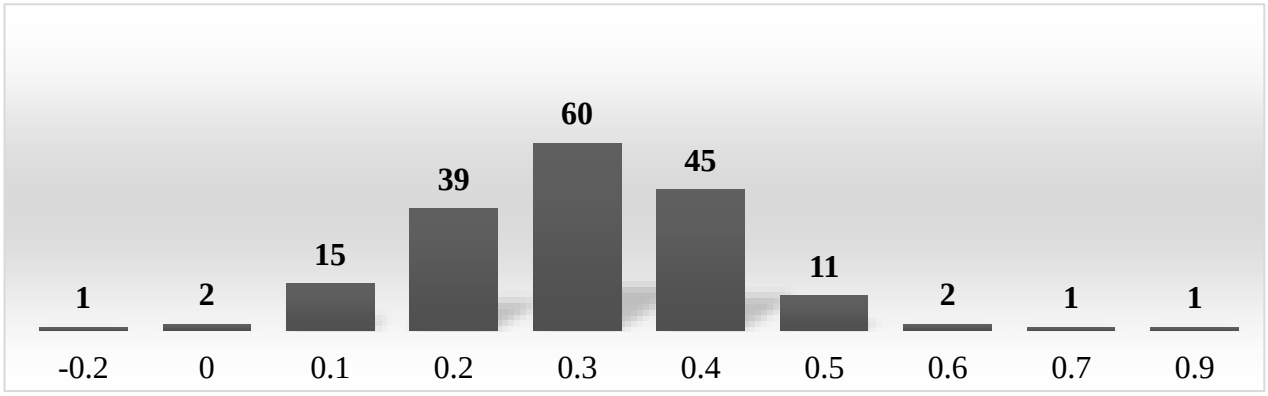


Figure 4-2: Change in INR during interval from admission to the end of the 12 h NAC infusion (SNAP).

Table 4-1 Clinical characteristics of patients with isolated INR elevation at the end of 12 h SNAP regimen

Variables	Discharge (75)	Repeat blood (68)	Continue NAC (34)	Total (177)
Sex (female %)	52%	72%	70.6%	70.6%
Age	22±21	22±12	24±32	22±18
Time to NAC [median (IQR)]	9±5	6 ±2	8±5	7±4
Time to NAC [N (%)] **≤ 16 h** **>16 h** **Unknown**	 59 (78.7) 7 (9.3) 9 (12)	 60 (88.2) 1 (1.5) 7 (10.3)	 27 (79.4) 3 (8.8) 4 (11.8)	 146 (82.5) 11 (6.2) 20 (11.3)
Dose (mg/kg) [median (IQR)]	200±146	222±139	277±238	214±140
Nomogram band [N (%)] **<150** **150 -300** **>300** **Unknown**	 41 (54.7) 16 (21.3) 7 (9.3) 11 (14.7)	 37 (54.4) 22 (32.4) 1 (1.5) 8 (11.8)	 5 (14.7) 18 (52.9) 7 (20.6) 4 (11.8)	 83 (46.9) 56 (31.6) 15 (8.5) 23 (13)
ALT at baseline [median (IQR)]	16±8	15±10	17±14	15±10
ALT at 12 h [median (IQR)]	16±10	13±7	23±13	16±11
ALT peak [median (IQR)]	18±13	16±11	27.5±24	18±12
INR at baseline [median (IQR)]	1.1±0.1	1.2±0.2	1.1±0.2	1.1±0.1
INR at 12 h [median (IQR)]	1.4±0.1	1.4±0.1	1.5±0.1	1.4±0.1
INR peak [median (IQR)]	1.4±0.1	1.4±0.1	1.5±0.3	1.4±0.1

Table 4-2: Changes in INR and ALT during NAC treatment for paracetamol overdose in patients with isolated INR increases (177 patients).

Variables	Before NAC therapy	After 12 h NAC infusion	P value
Time since overdose ingestion, (h)	7±4	21±5	-
INR	1.2±0.1	1.4±0.1	0.0001
Alanine Aminotransferase, IU/l	15±10	16±12	0.69

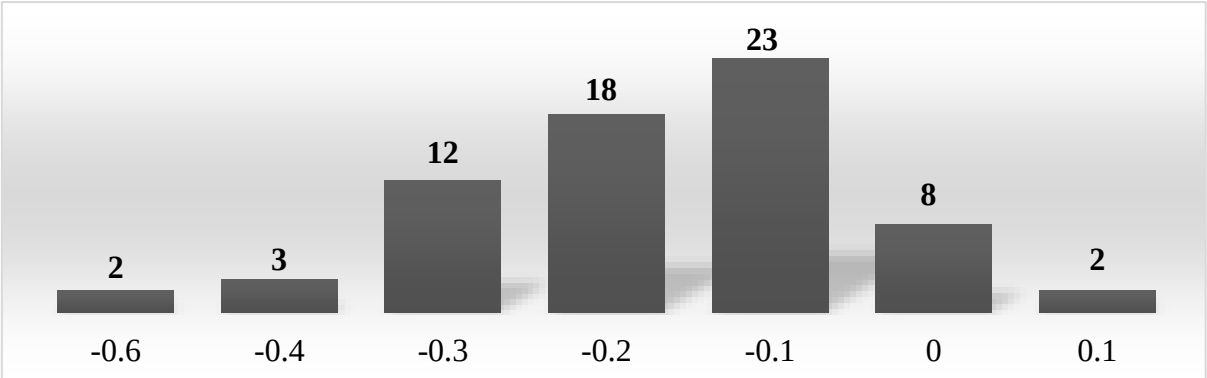


Figure 4-3: Change in INR during the interval from end of 12h NAC infusion (SNAP) to blood sampling (24 h post overdose).

Table 4-3: Changes in INR and ALT during NAC treatment for paracetamol overdose in patients with isolated INR increases, who had no additional NAC and had repeated bloods taken at 24 h post overdose (68 patients).

Variables	After 12 h NAC infusion	After 24 h post overdose	P value
Time since overdose ingestion, (h)	20±3	25±5	-
INR	1.4±0.1	1.3±0.2	0.0001
Alanine Aminotransferase, IU/l	13±7	13±11	0.90

4.4. Discussion

NAC is the antidote of choice to prevent hepatic injury in patients with paracetamol overdose; however, previous studies have showed that NAC can decrease the activity of coagulation factors without any sign of hepatocellular injury. Prothrombin time is routinely used to assess hepatic failure induced by paracetamol overdose; hence the impact of NAC on PT might lead to misinterpretation of the outcome in some patients. Use of the standard NAC regimen of NAC using a loading dose of 150 mg/kg infusion over 60 minutes was reported to diminish the coagulation activity, whereas there has not been a previous evaluation of the effect of the 12 h modified NAC regimen with its loading dose of 100 mg/kg infusion over 2 hours on coagulation time. In this study we

measured the impact of 12 h SNAP regimen on changes of INR during and after NAC infusion.

We found that INR significantly increased during NAC therapy by a median of 0.3 and it significantly decreased or remain unchanged when NAC was discontinued. within a median (IQR) time of 5.5±4.6 h.

This is in keeping with the findings that prothrombin time increases from 12 to 15 seconds (equivalent to 1 to 1.3 of INR value) after a median time of 7.7 h following initiation of the 21 h NAC regimen in patients with paracetamol overdose (166). NAC can interfere with coagulation activity shortly after starting treatment, but the maximal effect of the 21 h NAC regimen on prothrombin time occurs between 14 (160) and 16 hours (168) after the initiation of the NAC infusion with a 21% change of prothrombin time relative to the baseline, which is observed after three-quarters of the total standard NAC dose. In our study, the median INR increase in patients with normal ALT after 12h of NAC treatment using the SNAP protocol was 20%.

It has also been observed that the effect of NAC on coagulation factor activity is reversible and INR normalized after discontinuation of NAC infusion(169). In this study, we found that after discontinuation of the 12 h NAC infusion INR decreased within 6 h or remain unchanged in the majority of patients; although two patients had an increase in the INR from 1.4 to 1.5, this is likely to reflect assay variability rather than an actual increase in INR.

Although isolated INR elevation is linked to the NAC infusion, there is also the possibility that paracetamol itself can interfere with coagulation activity in the absence of hepatic failure (164). A therapeutic dose of paracetamol (4g daily) significantly increased the INR, but only after 4 days (30). A single paracetamol overdose of 24 g or more, however, can increase INR above the reference range within 12 to 16 hours without any sign of hepatic damage (161). In this study, NAC was started within 16 hours of paracetamol overdose in 82.5% of patients, so it is possible that the observed increase in INR might also be contributed to by paracetamol as well as NAC.

There are several limitations to this study. The majority of patients were treated with NAC within 16 h, so the impact of NAC on INR in those treated after 16 h could not be characterised. We therefore could not eliminate the possible effect of paracetamol on coagulation factors, which may have contributed to the INR rise. There was variability

in the timing of taking blood samples following the SNAP protocol which might also impact on our findings. The protocol advised to repeat post SNAP blood ≥24h after paracetamol intake (at least 4 to 6 hours from blood sample at the end of 12 h NAC infusion), to allow INR rise to be resolved after NAC discontinuation; we cannot therefore exclude that in some patients, the decline in INR after stopping NAC infusion might take longer than 6 hours.

4.5. Conclusions

The purpose of the current study was to determine the impact of the SNAP regimen on INR in patients with paracetamol overdose. The SNAP regimen increased the INR in the presence of normal liver function at the end of 12h NAC infusion, but the INR generally falls within 6 hours of NAC discontinuation. These results should be taken into consideration when interpreting the end-of-infusion blood results. It is recommended that unnecessary additional NAC treatment may be avoided by repeating the INR 4-6 hours later in patients with an isolated INR increase.

CHAPTER 5

DEVELOPMENT AND VALIDATION OF A CLINICAL DECISION RULE

Chapter 5 Development and validation of a clinical decision rule allowing earlier discharge of patients with paracetamol poisoning after a shorter 12-hour acetylcysteine (SNAP) protocol.

5.1. Introduction

The SNAP regimen is a modified 12h NAC infusion for the treatment of paracetamol overdose. Although the efficacy of the SNAP regimen appears to be similar to the standard regimen in most patients (134), it is still unclear which patients can be discharged at the end of the 2-bag, 12h regimen. The SNAP regimen was initially implemented in three hospitals in the U.K. and was recommended as an alternative to the standard regimen in June 2021(26) as an off-label regimen for use in patients with previous severe NAARs.

In the majority of patients with paracetamol overdose, it takes 10 to 20 hours for paracetamol to be completely eliminated from the body (170), although this can as long as 3 days in some patients who develop liver damage (171). Therefore, current practice is for the standard 16 hourly bag to be continued to avoid suboptimal treatment in those with ongoing detectable paracetamol or with abnormal laboratory tests. On the other hand, patients may be discharged if both liver function tests and paracetamol level are normal at the end of the NAC infusion(172). Nevertheless, the criteria for discharge at the end of the 21h NAC regimen are not well defined and vary between some institutions, for example, it is not routine clinical practice to check the paracetamol concentration at the end of the 21h infusion in the UK, which may be important in patients who take massive overdoses.

The abbreviated 12-h SNAP regimen appears to be safe and similarly effective compared to the standard regimen (134) but requires a simple clinical decision rule to facilitate the clinical decision to discharge. It has been reported that the 72-hour oral NAC treatment can be stopped if the serum paracetamol level is no longer detectable and aminotransferase levels are normal(173). Harrison et al claimed that the 72-hour oral NAC oral course can be shortened to 24 h or less if the patients had no evidence of hepatotoxicity within 36 h of overdose ingestion(174), however the reliability of early predictors of hepatotoxicity is unclear. Aminotransferases can be elevated up to three times the upper limit of normal without any clinical importance(170).

The SNAP protocol that was implemented in clinical practice in 2016 did not allow patients who were less than 24h post-ingestion at the time of the end of the 12h infusion to be discharged until they had another blood sample taken at least 24h post-ingestion (**Figure 5-2**). As a result, a group of patients being treated with the current SNAP protocol 2016 might be either treated with extra dose of NAC or remain in hospital until an additional blood test, which consequently increase the length and cost of hospital stay.

In this chapter, we aim to develop simple clinical decision rule based on existing treatment protocols for safe early patient discharge at the end of the 12h SNAP regimen.

Aim of this Chapter:

- Develop discharge criteria for clinical use using the current standard UK treatment nomogram.
- Validate the criteria using “early” and “late” blood results.
- Refine SNAP criteria for NAC continuation
- Simplify SNAP protocol for routine implementation

5.2. Methodology:

5.2.1. Study design and participants:

Patients admitted for treatment with paracetamol overdose in two hospitals in the U.K. from September 2016 to 2020 were treated with a 12h SNAP regimen. The decision to use this treatment was based on the revised paracetamol overdose treatment nomogram in UK (**Figure** 5-1), which starts at 100 mg/dl at 4 h, with an exponential decay in the treatment line to 12.5 mg/l at 16 h (half-life 4h). The decision to authorize a patient’s discharge was taken at least 24h post-ingestion in all patients in accordance with a SNAP treatment protocol that had been approved by local medicines management and governance committees (**Figure 5-2**).

We aimed to use the clinical data from this observational cohort of patients to develop a clinical decision rule for predicting which patients it would be safe to discharge at the end of the 12 h NAC SNAP regimen. We used the current standard UK treatment nomogram to develop potential clinical decision rules, and then used the data from patients’ medical records to validate the clinical decision rules.

5.2.2. SNAP protocol 2016:

The modified 12 h 'SNAP' regimen, consisting of intravenous NAC 100 mg/kg over 2 h then 200 mg/kg over 10 h, was introduced in 2016 in two U.K. hospitals to treat all patients requiring NAC for paracetamol overdose. NAC treatment was discontinued if all of the following criteria were met at the end-of-infusion ("early post-SNAP") sample (**Figure 5-2**):

ALT<80
ALT not more than doubled from admission
INR<1.3 and ALT<40 (upper limit of normal), and
paracetamol concentration <10 mg/L.

When this early post-SNAP sample occurred earlier than 24 h post-ingestion, an additional blood sample was taken at least 24 h post-ingestion ("late post-SNAP") sample. A further (3rd) infusion of NAC was given at 200 mg/kg over 10 h in patients who did not meet these criteria on either the early or late blood sample.

5.2.3. Clinical decision rule for discharge at 12h.

1. Refine criteria for patients needing additional NAC

   In those with paired blood tests, we refined the current SNAP criteria for continued NAC treatment at 24 h, using data taken from a small group of patients who, despite meeting the criteria for discharge at 12 h, subsequently also met current protocol criteria for NAC reinstitution on their 24h blood sample.

2. Development of clinical decision rules

   Criteria for early discharge of patients at 12 hours post NAC treatment (SNAP protocol 2016) included a paracetamol concentration threshold derived from the current standard UK treatment nomogram (**Figure** 5-1). The nomogram was developed originally for diagnosis and treatment, but not for determining safety for discharge from hospital. (175). The nomogram provides high reliability when paracetamol concentration is measured within 4 to 16 hours post overdose. At 16 hours post-ingestion, the risk of toxicity in patients who are not treated with acetylcysteine is estimated to be around 1 in 4400 patients

if the paracetamol concentration is below the treatment threshold of 12.5 mg/l (77) and these patients are considered safe to discharge without NAC treatment. Therefore, the paracetamol concentration together with normal liver function tests would indicate that it should also be safe to discharge patients who have already received a total dose of 300 mg/kg acetylcysteine, without further treatment.

We therefore started with the following criteria: paracetamol <10, ALT≤ 40 and INR<1.4 and developed additional clinical rules by changing cut-offs of INR, ALT and paracetamol iteratively.

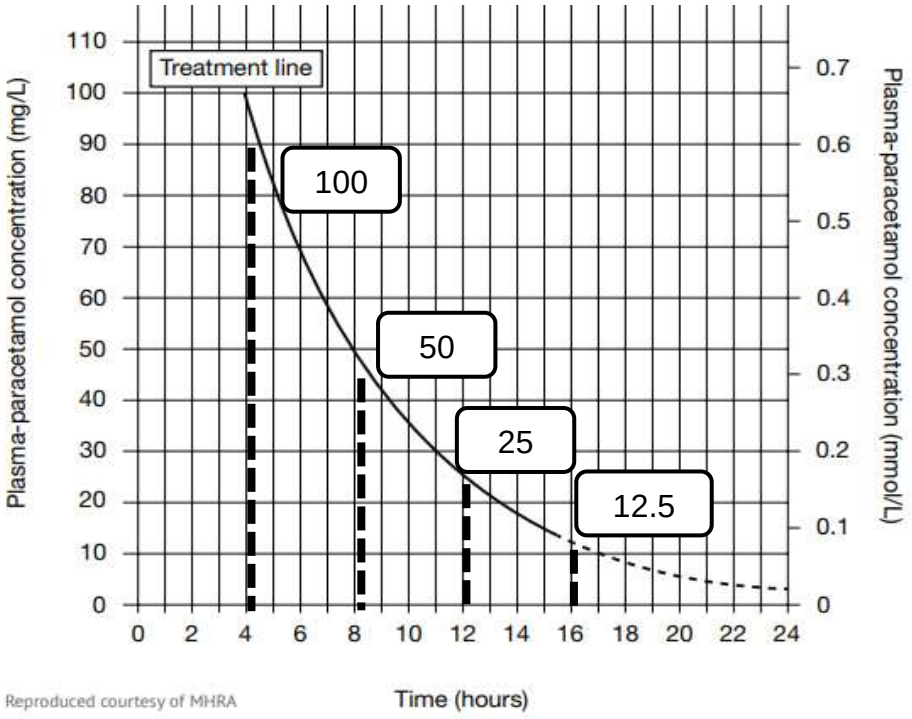


Figure 5-1: Paracetamol Treatment nomogram in UK

3. Selection and Validation phase

The accuracy of these criteria for safe patient discharge at the end of 12 NAC infusion was tested in our cohort of patients treated with the SNAP regimen.

We used patients who were eligible for discharge at least 24 hours post overdose ingestion to validate the predictive criteria. This validation process

should result in no patient eligible for discharge at 12 hours of the SNAP regimen meeting current criteria for restarting NAC at 24 hours.

We split the patients into two groups based on number of blood tests available for each patient:

1) those who had only a single blood sample taken late (24 h post-overdose) and were discharged safely without further treatment based on the current SNAP protocol 2016. We then determined the proportion of patients who would be eligible for discharge if the suggested criteria were applied at 12 hours post-infusion.
2) patients in whom there were paired “early” (12 h post-infusion) and “late” (24 h post-overdose) samples. Each suggested decision rule was applied at 12 hours in each patient to determine whether it was predictive of who could be discharged based on the 24 hour blood sample.

4. Revise and simplify the current SNAP protocol 2016 to allow safe implementation in routine clinical practice.

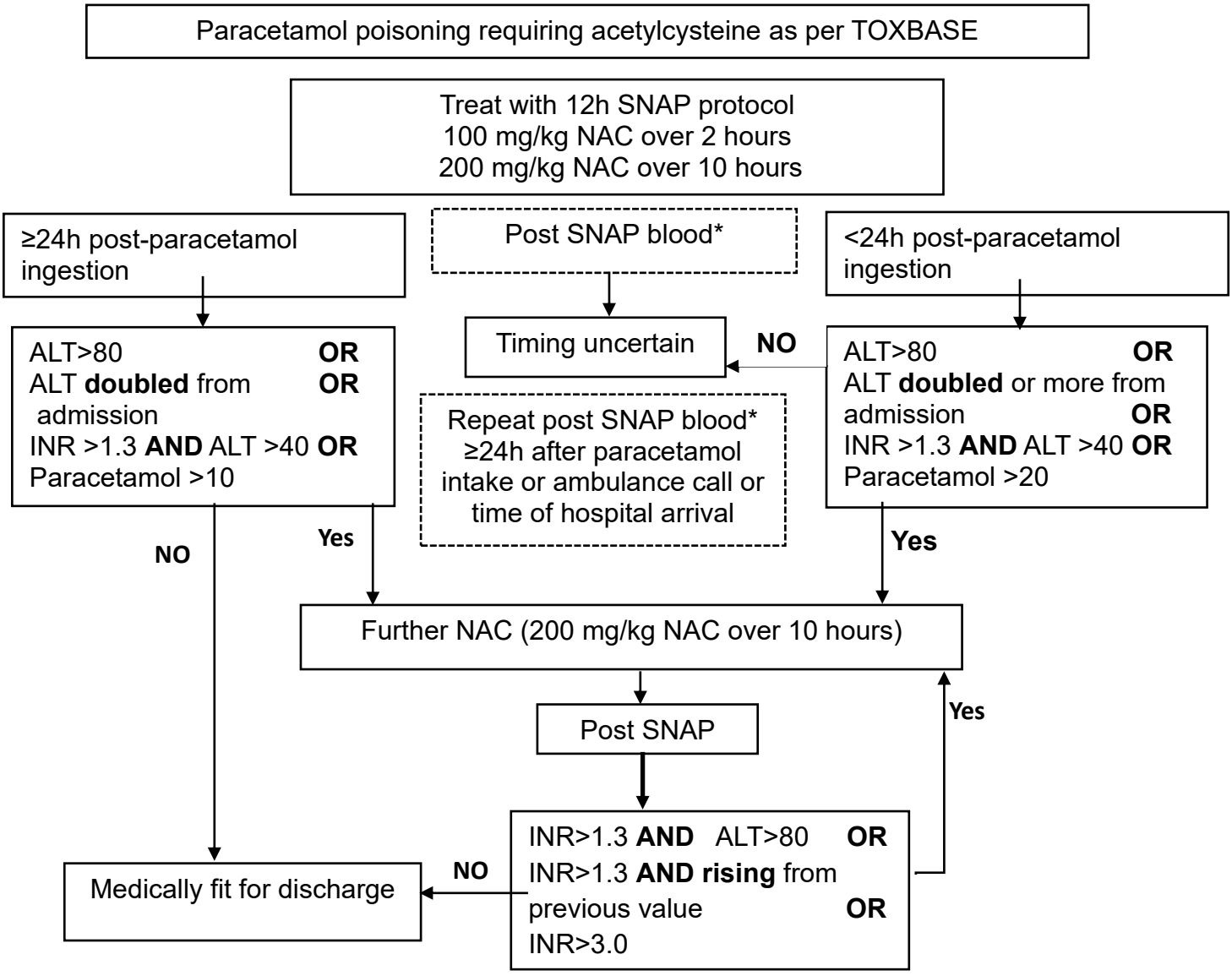


Figure 5-2: A clinical protocol for patients treated with the SNAP regimen 2016.

5.2.4. Laboratory measurements:

The potential predictive criteria were created based on the clinical laboratory measurements that were recorded at admission and at the end of NAC infusion: ALT (IU/L), INR, and paracetamol concentration (mg/L). The upper limit of the normal range for ALT in the RVI and St Thomas Hospital is 40.

5.2.5. Statistical analysis:

A descriptive analysis was carried out, based on the absolute or relative frequencies as percentages using data in patients in the RVI, Newcastle and St Thomas Hospital, London. Edinburgh data were not included in the analysis for this section as the SNAP protocol used was slightly different in terms of the criteria used.

To assess the predictive accuracy of the rule, we constructed a 2×2 table for calculation of the following: sensitivity, specificity and positive (PPV) and negative predictive values (NPV).

Receiver operating characteristic curves (ROC) were used to represent graphically the relative probability of clinical rule models to predict hepatotoxicity and hepatic injury outcomes. We develop the prediction model derived from the criteria variable of the model using binary logistic regression in SPSS data set. The best possible model would be a probability of true positive (sensitivity) of one with the probability of a false positive of zero (1-specificity). The area under the curve was also calculated for the prediction, so the best model would have area under the curve of 1.0, and the worst possible model of 0.5 or lower.

Data management and statistical analyses were performed using SPSS (version 25) software.

5.3. Results:

Of 1868 patients treated with the SNAP regimen, 218 patients were excluded due to missing values for either INR, ALT, and/or paracetamol concentration at the end of 12h SNAP regimen.

Of the 1650 patients with available blood tests for analysis, 961 patients had single blood tests at the end of 12 h NAC infusion and 689 had paired blood samples.

1. Refining the criteria for NAC continuation at 24h

Of the 689 patients with paired blood samples, 126 (18.3%) met the criteria for NAC continuation at 24h, of which 70 had a doubling of ALT at 12 h from admission.

In 7 patients, the ALT at 24h doubled or more from admission but remained within the normal range (ALT ≤40 IU/l) (**Table 5-1**).

Table 5-1: Patients with ALT at 24 h doubled or more from admission but remaining within the normal range.

		Admission		12h			24h			Peak		Total
Patient	Dose Type	ALT	INR	ALT	INR	Para-cetamol	ALT	INR	Para-cetamol	ALT	INR	No. Bag
1	Acute	10	1.0	13	1.1	11	20	1.2	5	20	1.2	2
2	Acute	8	1.0	10	1.2	29	16	1.1	5	16	1.3	2
3	Acute	15	1.0	16	1.2	11	34	1.2	5	34	1.2	3
4	Acute	17	1.0	48	1.2	5	34	1.3	5	48	1.3	3
5	Acute	12	1.0	24	1.5	7	30	1.4	5	30	1.5	2
6	Acute	18	1.0	32	1.3	5	39	1.2	5	39	1.3	2
7	Acute	12	1.1	17	1.3	23	28	1.4	5	85	1.4	5

As a result of this, we refined the criteria for NAC continuation at 24h as shown in **Figure** 5-3. These criteria were also adopted as applicable at the end of the standard 21h regimen on TOXBASE in October 2021.

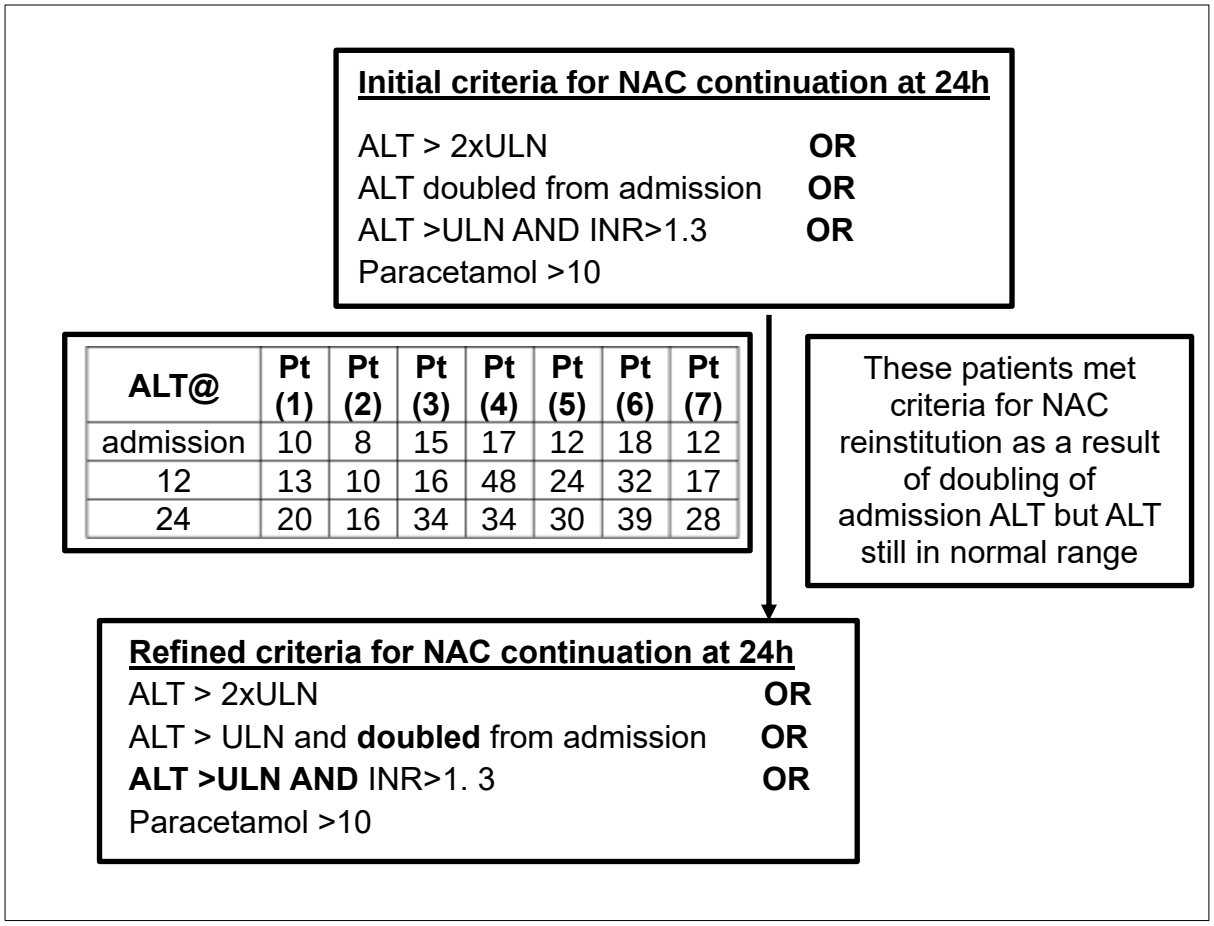


Figure 5-3: Refined criteria for patients needing additional NAC

2. Development of clinical prediction rules for safe discharge at end of 12h SNAP

shows six potential clinical criteria for discharge at 12h were developed from the UK revised paracetamol overdose treatment nomogram (**Figure** 5-1).

Table 5-2: Clinical prediction decision rules developed from paracetamol overdose treatment nomogram.

Potential criteria for early patients discharge at the end of the 12 h SNAP regimen:

1. **Paracetamol <10, ALT≤ 40, INR≤ 1.3**
2. **Paracetamol <10, ALT ≤ 50, INR≤ 1.3**
3. **Paracetamol <10, ALT ≤ 40, INR≤ 1.4**
4. **Paracetamol <20, ALT ≤ 40, INR≤ 1.3**
5. **Paracetamol <10, ALT≤ 40, ALT doubled or more from admission**
6. **Paracetamol <10, ALT≤ 40, ALT not doubled or more from admission AND INR≤ 1.3**

3. Selection of decision rules in patients with single (early) post NAC sample

When applying each of the clinical decision rules in **Table 5-2** to the 961 patients with a single blood test (**Table 5-3**). Clinical prediction rules (3) and (5) predicted the highest proportions of patients that would be eligible for discharge at 12 h post SNAP treatment. These were therefore selected for validation against the actual outcome using the current SNAP protocol 2016.

No patients meeting criteria (5) at 12h post-infusion met the criteria for NAC continuation at 12h based on the SNAP protocol 2016. There were 228/961 (23.7%) patients who did not meet the criteria (5) for discharge at 12 h (**Table 5-3**), of which 133/228 required further NAC treatment based on the current SNAP protocol 2016. These patients had a single blood sample despite requiring further NAC treatment because they either self-discharged before or after receiving additional NAC (127), were transferred to liver unit (5), or died (1).

There were five patients meeting criteria (3) at 12h post-infusion who would have required NAC continuation at 12h based on the current SNAP protocol 2016 (**Table 5-4**). All 5 had ALT values that had doubled or more since admission, but these still all remained within normal limits (**Table 5-4**).

Table 5-3: Predicted outcomes of different 12h treatment discontinuation criteria when applied to 961 patients with a single blood result at 12h

Potential criteria applied at 12h post-NAC	Predicted outcomes at 12 h post NAC infusion based on criteria	
	Discharge	**No discharge**
1. paracetamol <10, ALT≤ 40, INR≤ 1.3	690/961 (71.8)	271/961 (28.2)
2. paracetamol <10, ALT ≤ 50, INR≤ 1.3	719/961 (74.8)	242/961 (25.2)
3. paracetamol <10, ALT ≤ 40, INR≤ 1.4	744/961 (77.4)	217/961 (22.6)
4. paracetamol <20, ALT ≤ 40, INR≤ 1.3	705/961 (73.4)	256/961 (26.6)
5. paracetamol <10, ALT≤ 40, ALT not doubled or more from admission	733/961 (76.3)	228/961 (23.7)
6. paracetamol <10, ALT≤ 40, ALT not doubled or more from admission AND INR≤ 1.3	662/961 (68.9)	299/961 (31.1)

Table 5-4: Patient's characteristics that required NAC at 24 based on SNAP protocol

Patients	Dose Type	ALT adm	INR adm	Para adm	ALT 12	INR 12	Para 12
1	Acute	11	1	130	31	1.2	5
2	Acute	16	1	178	34	1.4	5
3	Acute	11	1.1	196	36	1.4	5
4	Staggered	10	1.1	43	21	1.3	5
5	Staggered	8	1.1	10	23	1.2	5

At this stage, clinical prediction rule 5 appeared most promising, allowing 76.3% to be discharged with no patients meeting criteria for NAC continuation.

4. Validation on patients with paired (early and late) blood samples

The potential clinical decision rules in **Table** 5-2 were applied on 689 patients with paired blood test. **Table 5-5** shows the predicted outcomes of these patients when the decision rule is applied at 12h post-NAC together with the actual outcomes of those who meet the criteria for discharge at 12h when the current criteria for NAC continuation (paracetamol concentration >10 mg/L; ALT 41-80 and INR>1.3; ALT doubled or more from admission; ALT>80) are applied on the late blood sample.

Table 5-5: Outcomes of patients with paired blood sample (689)

Criteria	Outcome according to blood sample results			
	Predicted Outcome when applied at 12 h (n=689)		Validated outcome of those meeting criteria for discharge on 12h sample based on late blood sample	
	No discharge	Discharge	No discharge*	Discharge
1. Para<10, ALT≤ 40, INR≤ 1.3	300(43.5%)	389(56.5%)	5 (1.3%)	384(98.7%)
2. Para<10, ALT ≤ 50, INR≤ 1.3	284(41.2%)	405(58.8%)	7(1.7%)	398(98.3%)
3. Para<10, ALT ≤ 40, INR≤ 1.4	258(37.4%)	431(62.6%)	7(1.6%)	424(98.4%)
4. Para<20, ALT ≤ 40, INR≤ 1.3	273(39.6%)	416(60.4%)	8 (1.9%)	408(98.1%)
5. Para<10, ALT≤ 40, ALT not doubled or more from admission	261(37.9%)	428(62.1%)	8(1.9%)	420(98.1%)
6. Para<10, ALT≤ 40, ALT not doubled or more from admission AND INR≤ 1.3	328(47.6%)	361(52.4%)	4(1.1%)	357(98.9%)

*Met the criteria for current NAC continuation: paracetamol concentration >10 mg/L; ALT 41-80 and INR>1.3; ALT doubled or more from admission; ALT>80

Of the 689 patients with paired (12 h and 24 h) blood tests, 428/689 (62.1%) met all of the following criteria (criteria 5) on the “early” (12 h post-infusion) blood samples: paracetamol<10, ALT≤ 40, ALT not doubled or more from admission (Table 5-5). Eight of these patients met one or more of the criteria for NAC continuation at 24h post-overdose (Table 5-6). Of these, one developed liver injury (ALT>100) on

subsequent blood sample, but non developed sever hepatotoxicity (ALT>1000 or INR>2).

Table 5-6: Patient's characteristics that met criteria for NAC continuation at 24h based on current protocol when using clinical decision rule 5 at 12h

		At adm		At 12 h			At 24h			Peak		Total No. Bag
Patients	Dose Type	ALT	INR	ALT	INR	Para	ALT	INR	Para	ALT	INR	
1	Acute	18	1.1	26	1.5	5	83	1.3	5	91	1.5	3
2	Acute	49	1.1	40	1.4	5	52	1.4	5	52	1.4	3
3	Acute	12	1.3	22	1.7	5	66	1.6	5	77	1.7	4
4	Acute	18	1	32	1.3	5	39	1.2	5	39	1.3	2
5	Acute	42	1	37	1.1	5	85	1.1	5	85	1.1	2
6	Staggered	18	1	15	1.2	5	65	1	5	125	1.2	4
7	Staggered	14	1	24	1.4	5	113	1.3	5	113	1.4	3
8	Chronic	24	1	22	1.1	5	49	1	5	49	1.1	2

Three patients (number 4, 5 and 8) were discharged after at least 24 h since overdose without any further treatment, while 5 patients (1, 2, 3, 6 and 7) received additional NAC.

Patient numbers 1 and 7 got a third bag, as ALT went to above 80 IU/L. The peak ALT in these 2 patients were 91 and 113 respectively.

Patient numbers 2 and 3 got additional NAC as the ALT increased to more than 40 IU/L and INR increased to greater than 1.3. The peak ALT was 52 and 77.

Patient number 6 had received extra NAC treatment just after the 24 h blood sample.

INR was unchanged or fell in all of these patients at 24h. It is therefore debatable whether any of these patients require additional treatment given the minor subclinical rise in ALT.

When applying clinical decision rule 3 (paracetamol <10, ALT ≤ 40, INR≤ 1.4), 431 patients (62.6%) met these criteria on "early" (12 h post-infusion) blood sample **(**Table 5-5). 7/431 (1.6%) of these patients met one or more of the criteria for N AC continuation at 24h post-overdose. One of these patients developed liver injury (ALT>100) on their 24 h blood sample, but none developed severe hepatotoxicity (ALT>1000 or INR>2). Details of these seven patients are provided in **Table 5-7**.

Table 5-7: Patient's characteristics that met criteria for NAC continuation at 24h based on current protocol when using clinical decision rule 3 at 12h.

		At adm		At 12 h			At 24			Peak		Total No.
Patients	Dose Type	ALT	INR	ALT	INR	APAP	ALT	INR	APAP	ALT	INR	
1	Acute	49	1.1	40	1.4	5	52	1.4	5	52	1.4	3
2	Acute	18	1	32	1.3	5	39	1.2	4	39	1.3	2
3	Acute	42	1	37	1.1	5	85	1.1	2	85	1.1	2
4	Acute	12	1	40	1.3	5	47	1.5	5	47	1.5	4
5	Staggered	18	1	15	1.2	5	65	1	5	125	1.2	4
6	Staggered	14	1	24	1.4	5	113	1.3	5	113	1.4	3
7	Chronic	24	1	22	1.1	5	49	1	2	49	1.1	2

Three of these patients were discharged at 24 h post overdose ingestion, without any further NAC treatment, whereas four had an extra NAC bag because the ALT doubled or more from admission (patient number 5), ALT was greater than normal and INR was above 1.3 (patient number 1 and 4), or ALT was greater than 80 (patient number 6) (see **Table 5-7**)

5. Revise current SNAP protocol 2016

Table 5-8 shows the predictive value of clinical decision rule 5: paracetamol <10, ALT≤ ULN, ALT not doubled or more from admission on our cohort.

No patients meeting these criteria at 12h subsequently developed ALT>1000. Seven patients developed an INR>2, of whom five were on either warfarin or enoxaparin, and two had an elevated INR due to either chronic alcoholic hepatitis or sepsis.

Table 5-8: Predictive Value of 12 h Clinical Decision Rule (5): paracetamol <10, ALT≤ ULN, and ALT not doubled or more from admission.

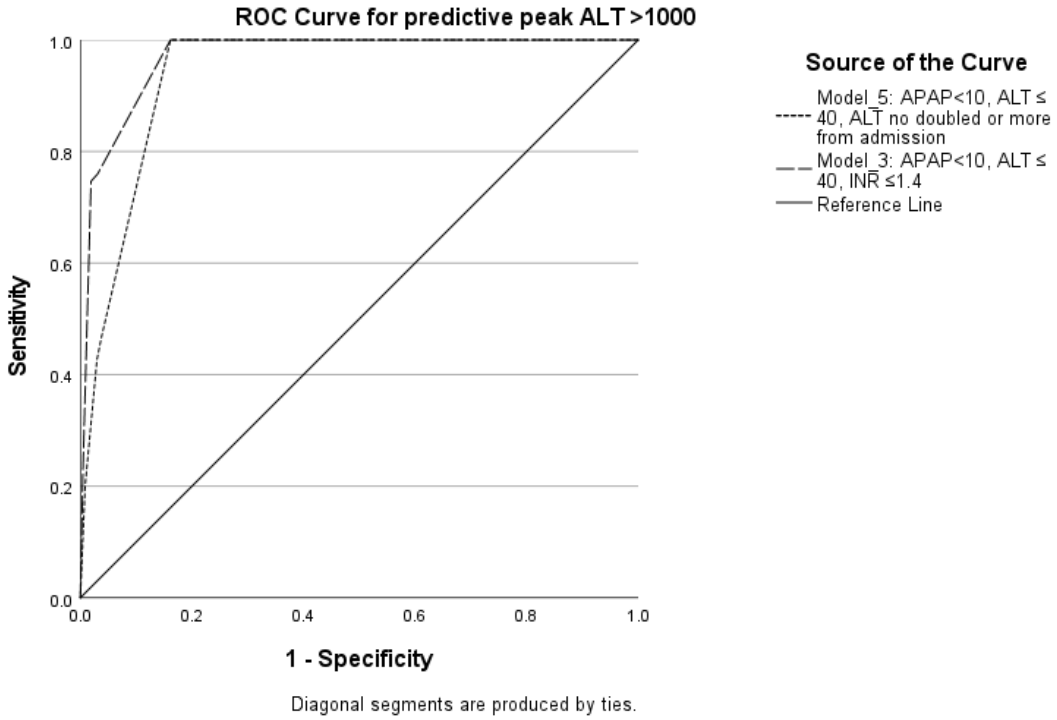
(APAP<10, ALT ≤ ULN, ALT not doubled or more from admission)		Peak ALT <80		Peak ALT<100		Peak ALT<1000		Peak INR <2	
		Yes	No	Yes	No	Yes	No	Yes	No
Met these criteria at end of 12 h NAC infusion	Yes N= 1161	1154	7	1158	3	1161	0	1154	7
	No N= 489	264	225	296	193	412	77	439	50
Sensitivity (%)		81.4		79.6		73.8		72.4	
Specificity (%)		97		98.5		100		87.7	
Positive predictive value (%)		99.4		99.7		100		99.4	
Negative predictive value (%)		46		39.5		15.7		10.2	

Table 5-9 shows the predictive value of clinical decision rule 3: paracetamol <10, ALT ≤ 40, INR≤ 1.4 (see **Table 5-9**). No patients meeting these criteria at 12h developed ALT>1000. Two developed an INR>2: one was due to warfarin, and another due to sepsis.

Table 5-9: Predictive Value of 12 h Clinical Decision Rule (3): paracetamol <10, ALT≤ ULN, and INR≤ 1.4

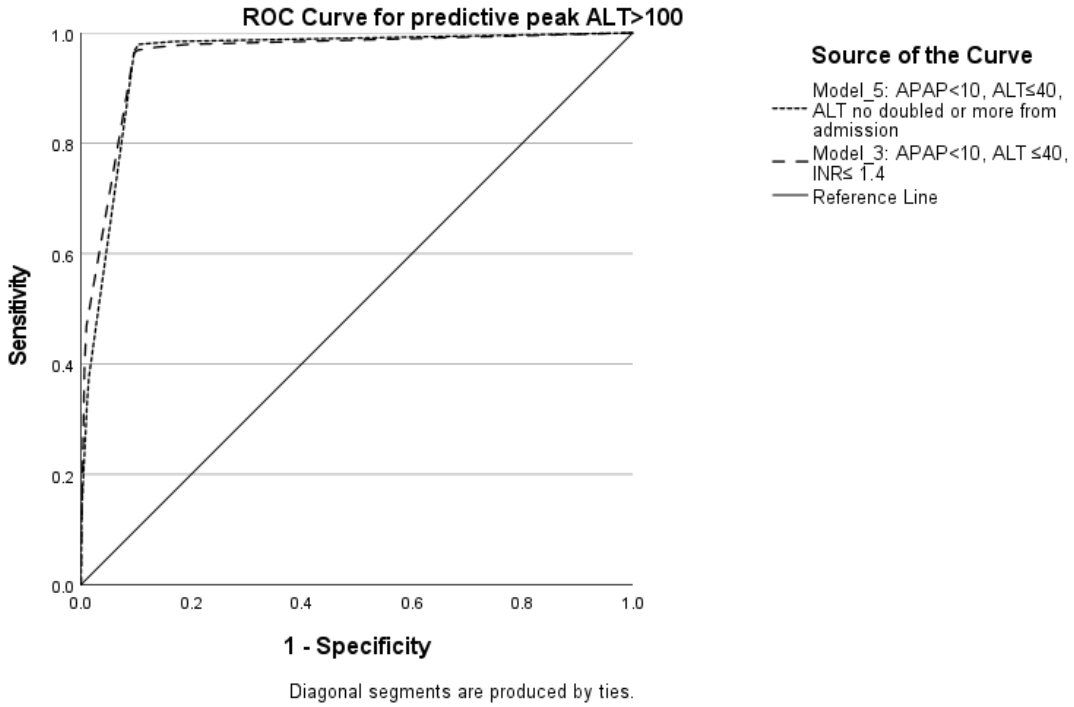
(Paracetamol<10, ALT ≤ ULN, INR ≤ 1.4)		Peak ALT <80		Peak ALT<100		Peak ALT<1000		Peak INR <2	
		Yes	No	Yes	No	Yes	No	Yes	No
Met these criteria at end of 12 h NAC infusion	Yes N= 1175	1168	7	1171	4	1175	0	1173	2
	No N= 475	250	225	283	192	398	77	420	55
Sensitivity (%)		82.4		80.5		74.7		73.6	
Specificity (%)		97		98		100		96.5	
Positive predictive value (%)		99.4		99.7		100		99.8	
Negative predictive value (%)		47.4		40.4		16.2		11.6	

ROC curves (**Figure 5-4** and **Figure 5-5**) show the discrimination of decision rules 3 and 5 to predict the outcomes of hepatotoxicity (peak ALT >1000) and hepatic injury (peak ALT >100) in our cohort.



Area Under the Curve			
Test Result Variable(s)	**Area**	**P-value**	**Absolute Difference (95%CI)**
Model_5	0.940	0.000	0.926 to 0.954
Model_3	0.970	0.000	0.959 to 0.981

Figure 5-4: Receiver operating characteristic curve (ROC) for comparing the ability of model 5 and model 3 to identify patients who subsequently develop hepatotoxicity (ALT peak >1000 IU/L) after discharge at 12 h post SNAP treatment.

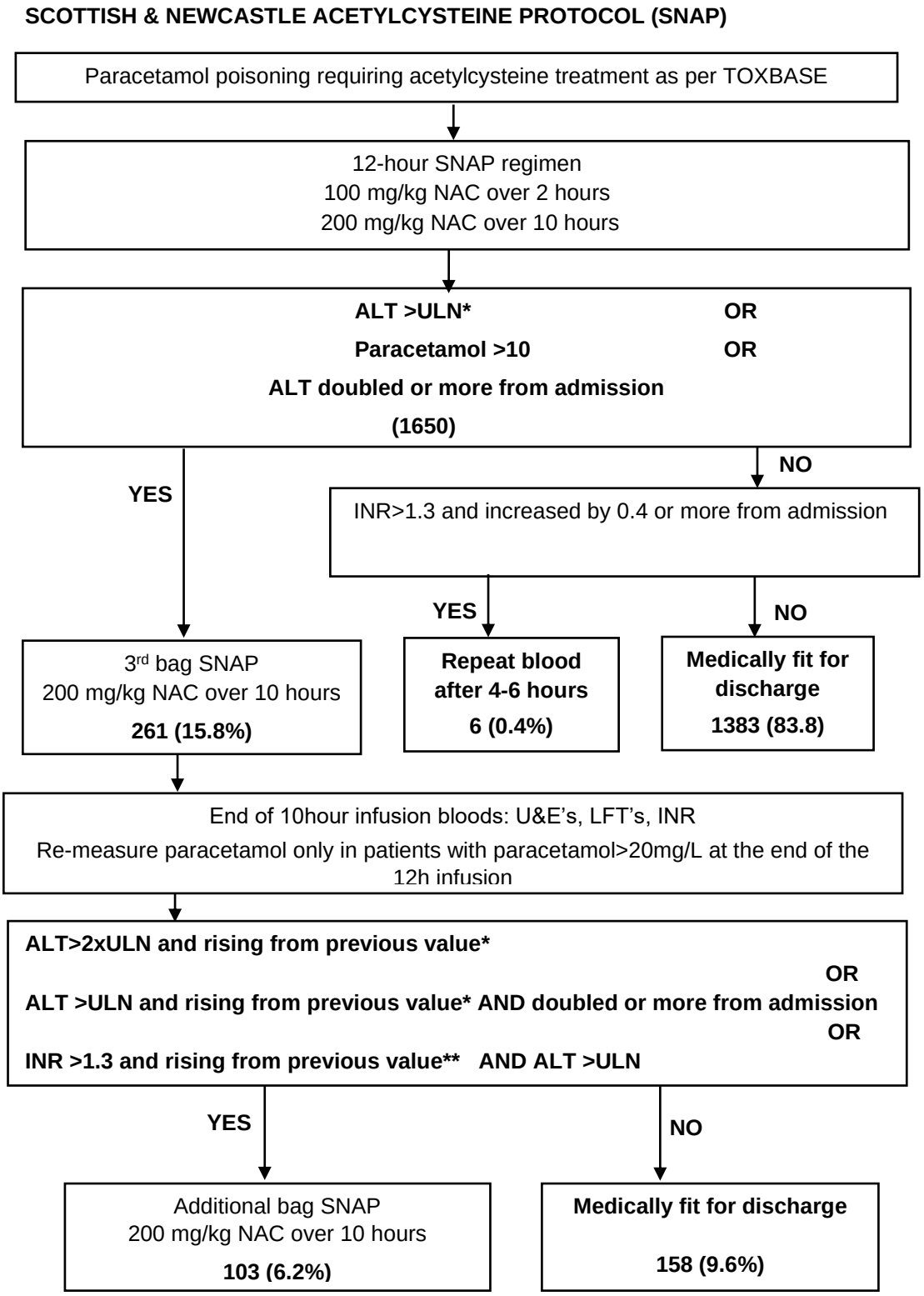


Area Under the Curve			
Test Result Variable(s)	**Area**	**P-value**	**Absolute Difference (95%CI)**
Model_5	0.954	0.000	0.943 to 0.972
Model_3	0.957	0.000	0.941 to 0.968

Figure 5-5: Receiver operating characteristic curve (ROC) for comparing the ability of model 5 and model 3 to identify patients who subsequently develop hepatotoxicity (ALT peak >100IU/L) after discharge at 12 h post SNAP treatment.

Based on these results, we revised the 12-hour SNAP protocol 2016 and constructed a simplified flow chart for clinical implementation (**Figure 5-6**). This uses clinical decision rule 5 at the end of 12h but also takes into account the impact on INR as discussed in chapter 4. We considered this to be preferable to clinical decision rule 3 which includes an INR>1.4. Continuation of NAC in these patients is likely to lead to a persistent elevation of INR.

Using our cohort of 1650 patients, we applied this revised protocol to predict the disposition of patients treated with the 12h SNAP regimen. This is also shown **Figure 5-6**. We therefore expect that with this revised protocol, 83.8% of patients will be eligible for discharge at the end of 12h.



* in patients with chronically elevated ALT, NAC may be discontinued if the ALT is abnormal but unchanged or fallen from the previous value

**in the absence of another cause e.g warfarin

Figure 5-6: Simplified SNAP Flow Chart using decision rule 5: ALT>40, Paracetamol >10, ALT doubled or more from admission).

5.3.1. Care pathway

It has been highlighted that treatment of paracetamol overdose with NAC requires complex calculations, introducing a risk of error even when this is done by trained practitioners. Therefore, a clinical care pathway or chart has been proposed to the reduce the error risk (176). Most NAC treatment is initiated in the emergency department (ED), where the prescriptions are not routinely checked by pharmacists. In one study errors made in NAC dose calculations were reduced from 26% to 0% if a dosing chart was used (176). As well as inaccurate dosing, infusion rate errors, interruption treatment, or unnecessary assay administration are also common errors during treatment with NAC infusion (89). The most common error associated with NAC treatment is interruption of treatment. In one study 68% patients had an interruption in treatment of more than one hour which could worsen treatment outcomes and also delay hospital discharge(92).

Although the SNAP regimen is simpler than the original dosing regimen, accurate NAC dose calculation is still required (176). A stepwise management of acute paracetamol overdose can facilitate evidence-base healthcare. Therefore it is to be expected that a care pathway, which standardises clinical practice guideline recommendations into a clinical process, would maximize clinical efficacy and reduce errors related to NAC dosage(177). An integrated care pathway has been shown to improve the management of patients with paracetamol overdose treated with the 21h NAC regimen(178). Therefore, we also designed SNAP care pathways for adults and children (less than 6 years) to facilitate implementation of SNAP into clinical practice, see **Appendix (B)**.

5.4. Discussion:

The abbreviated 12 h NAC (SNAP) regimen was recently added to UK guidelines as an alternative NAC regimen for the treatment of paracetamol overdose. Precise clinical criteria for safe discharge at the end of the 12-hour SNAP treatment have not yet been defined, so the current SNAP protocol relies on extra precautionary measures and repeat blood sampling at 24h, which complicates clinical decision-making and delays discharge. Therefore, clear and simple criteria for safe early patient discharge after the 12h SNAP regimen are important for facilitating the use of this regimen in routine

clinical practice and maximising the savings in terms of hospital stay and bed occupancy.

We have showed that the application of the following current SNAP clinical decision rule at 12h blood sample: Paracetamol<10, ALT≤ ULN, ALT not doubled or more from admission would lead to no patient developing hepatotoxicity in the current cohort. This clinical decision rule had one of two the highest number of patients that can be safely discharged after 12h (**Table 5-3**), had 100% capability to identify those who can be safely discharged at 12h post NAC treatment with no patient subsequently developing hepatotoxicity (peak ALT >1000IU/L) at 24h or more post overdose ingestion (**Table 5-8**). 3 patients qualifying for early discharge using this clinical decision rule developed minor hepatic injury 24 h post overdose with peak ALT not exceeding 150 and associated with a fall in INR (**Table 5-7**).

All patients who met the criteria for discharge at 12h using this decision rule but required more NAC treatment at 24h post overdose ingestion because of high INR rather than high ALT or paracetamol had INR falling or unchanged, which indicates the impact of paracetamol and NAC on INR elevation are not related to hepatotoxicity. Nevertheless, it is possible that some patients may develop a transaminitis post-discharge after the SNAP regimen.

While it is possible that a short duration of NAC might miss some patients with delayed development of hepatotoxicity as elevation of the transaminase level can take up to 48 hours to be observed(179), the risk of fulminant hepatic failure and death is minimal. In most patients (75%) with severe liver toxicity, an elevated transaminase can be noticed early within 24 hours of paracetamol ingestion(179). In Rocky Mountain Poison and Drug Centre in Colorado, US, the toxicologists believe that the 21h standard regimen might too short for patients who had massive overdose or hepatic injury at presentation, so they recommended to re-measure paracetamol and continue NAC treatment in those patients with high risk of hepatic injury. (146) This approach is embodied in the proposed SNAP protocol.

We first presented a preliminary proposal in 2018 (conference abstract 3 in Appendix A) for a simple 12h clinical decision for discharge which included a combination of clinical decision rules 3 and 5 in this chapter: paracetamol<10, ALT not doubled or more from admission, ALT normal and INR 1.4. As discussed in chapter 4, both

paracetamol (162) and NAC (166) may elevate INR unrelated to hepatic injury. INR elevation as early as 12 to 16 hours post exposure is likely to be due to paracetamol overdose as a result of reduction in factor VII (161). Although both criteria (5) and (3) were equally in identifying patients who can be safely discharged at 12h post SNAP treatment, criteria 3 includes a normal INR which is difficult to interpret because NAC can increase the INR. Therefore, criteria 5 was preferred to predict those who can be safely discharged at 12h of SNAP treatment in all patients, even though perfect criteria that will work in all circumstances do not exist in clinical practice. The median INR rise due to either NAC or paracetamol with the 21h protocol (166), and in with the SNAP regimen is 0.3. Therefore, we suggest that those with an isolated increase in INR by ≤0.4 from previous value and with no evidence of hepatic injury just need further observation and re-measurement of the INR at least 24 h post exposure instead of immediate provision of further NAC treatment.

We also observed that the criterion of doubling of ALT for NAC continuation is not useful for patients who are admitted with ALT lower than 20 IU/L. All 7 patients who had ALT doubled or more from admission, but where the ALT remained in the normal range were not at risk of hepatic injury or toxicity. Therefore, the criteria for NAC continuation at 24h were modified to add (ALT>40) as an additional requirement to the doubling in ALT from admission in the current standard criteria for NAC continuation in TOXBASE. However, as all patients who had a doubling or more in ALT at the end of the 12h SNAP regimen were treated with additional NAC; we have therefore opted to include this in the clinical decision rule as an added safety measure for patients whose ALT is rising rapidly despite being normal.

A paracetamol concentration of less than 10 mg/l is below the concentrations usually observed during therapeutic dosing (10-20µg/ml) (180-182). This concentration is deemed to be safe for discharge when it is also associated with no evidence of liver toxicity i.e normal ALT. This is already accepted as being safe in patients who take staggered paracetamol overdoses and are started immediately on NAC. If the paracetamol<10 and ALT normal at least 4 hours since the last ingestion, NAC may be discontinued. It is reasonable that such an approach can be safely applied to acute single overdoses 12h after NAC treatment.

While the current SNAP protocol is advised in TOXBASE to be used for patients with experience of NAARs, this simplified version has been constructed use in all patients (**Figure 5-6**). In November 2021, the Royal College of Emergency Medicine issued a position statement recommending the SNAP regimen as standard of care in emergency departments in the UK and highlighted its attractions in terms of reduced adverse event and reduced length of stay(183). They recommended that clinicians follow advice provided on TOXBASE. The protocol that we have developed in this study is currently being reviewed by the Clinical Standards Group of the National Poisons Information Service with a view to it being provided on TOXBASE for the management of paracetamol overdose.

There are several limitations to this study. There were very few patients with massive overdose of paracetamol in our cohort and therefore we are unable to ascertain whether this protocol is appropriate for this group of patients. Despite the large size of our cohort, we cannot exclude that hepatotoxicity may be delayed in rare circumstances. However, given that these criteria match those on the UK treatment nomogram at 16h when patients do not require NAC treatment at all as development of hepatotoxicity is considered unlikely, these criteria are likely to be reasonable in a group of patients who have already been treated with NAC.

5.6. Conclusion:

A simple clinical decision rule: paracetamol <10, ALT≤40, and ALT not doubled or more from admission accurately identifies low-risk patients who can be discharged safely after a shorter 12 h SNAP regimen. Use of these criteria will facilitate early discharge and reductions in length of hospital stay.

Chapter 6

DISCUSSION AND CONCLUSIONS

Chapter 6 Discussion and conclusion

6.1. Overview

Intravenous acetylcysteine (NAC) is the antidote of choice for treatment of paracetamol overdose. The 21h three-bag regimen, which has been modified from the original 20.25 h by Prescott in 1977 is the currently licensed regimen in the UK. Although the safety and efficacy of this regimen has been proven over the past 40 years, the regimen also established some drawbacks. NAARs are very common in the first hours of NAC treatment in patients' treatment with 21h regimen, and is strongly correlated to the high initial NAC concentration. The regimen is also associated with high reported rate of errors in preparation and dose calculation due to its complexity. A 12h two-bag (SNAP) regimen is associated with significantly fewer NAARs reported compared to 21h regimen.

This is the first large cohort study to evaluate the effectiveness of SNAP regimen compared to the standard regimen in all risk group of patients with paracetamol poisoning. Although preliminary evidence of safety and efficacy was reported by Pettie et al in 2019, its efficacy in all sub-groups of patients including late presenters and large overdoses is not yet clear. This research was also designed to develop a simpler protocol for safe discharge of patients at the end of 12h SNAP protocol and allow routine implementation in practice.

6.2. Main findings

1.1. In chapter 2, the pharmacokinetic simulation of SNAP regimen based on three compartment model indicated that the peak concentration was significantly lower compared to the conventional regimen but that continuation of the 200 mg/kg infusion after the first 12 hours was likely to maintain steady NAC concentrations. Importantly, discontinuation of the infusion for up to 4 hours was unlikely to cause concentrations of NAC to become undetectable. This provided the basis for a protocol consisting initially of a 12h regimen providing 300 mg/kg NAC, with the option of extending by a further 10 hours with a total NAC dose of 500mg/kg for selected patients.

2. In chapter 3, we evaluated the effectiveness of SNAP regimen in prevention of hepatotoxicity in a large cohort of patients treated for paracetamol overdose. 2946 patients were treated with the SNAP regimen and 1795 patients with the standard 21h regimen. Overall, the development of the primary outcome of hepatotoxicity as defined by a peak ALT>1000 was comparable in the SNAP and conventional regimen. In acute single overdoses, when treatment with NAC was initiated more than 16h post-overdose, the SNAP regimen appeared to be inferior (13% vs 4.8%, P=0.018), but when corrected for confounding factors, this difference disappeared (adjusted OR 1.3, 95% CI 0.33 to 5.16, P= 0.69). This is likely to be due to the low rate of hepatotoxicity in the control 21h NAC group, potentially due to bias in data collection from the retrospective nature of the study. We also showed that the main predictors of a peak ALT>1000 were: abnormal ALT at baseline, APAP*AT product>1500, nomogram band>150, and dose more than or equal 300mg/kg. In patients taking large overdoses (nomogram band>300), the rate of hepatotoxicity was not significantly different between the two regimens. There was also no difference between the SNAP and conventional regimen in the rate of development of hepatotoxicity in patients with staggered overdose and therapeutic excess. As a result, the study now provides additional evidence that the SNAP regimen is comparable in efficacy to the 21h regimen in all patterns of overdose.

3. In chapter 4, we demonstrated the impact that the SNAP regimen has on INR in the absence of liver injury with a median increase from admission to end-of-12 h infusion of 0.3, but the INR fell or was unchanged after 6 hours of NAC discontinuation in the majority of patients.

4. In chapter 5, we derived a simple decision rule for early patient discharge after the 12h SNAP regimen in all patients: paracetamol <10, ALT≤ ULN, ALT not doubled or more from admission. This was validated in a sub-cohort of 700 patients with 2 blood samples and no patient meeting these discharge criteria subsequent developed ALT >1000.

6.3. Clinical relevance

Paracetamol overdose is a common presentation to emergency departments in the UK, accounting for around 100,000 presentations annually. Around 50-60% of these require treatment with acetylcysteine. This study builds on the evidence provided by Pettie et al that the SNAP regimen is safe and effective (134) and provides additional information on efficacy in high-risk patients such as late presenters and large overdoses. More importantly, we developed a simple 12h protocol and care pathway which can be easily implemented in emergency departments and acute medical units to facilitate treatment and early discharge.

Given that NAC is such an effective antidote, showing superiority in particular sub-groups is very difficult. There are theoretical reasons why a higher dose of NAC may be more effective in patients who take a very large overdose, although there is some controversy over the whether it has a meaningful effect on important clinical outcomes such as development of liver failure and deaths. The data presented with the SNAP regimen in large overdoses is comparable to those of the study in Australia comparing the double-dose Australian regimen (200mg/kg over 4 hours, 200mg/kg over 16hours) in patients ingesting more than 35g paracetamol and whose paracetamol concentrations are above the 300-nomogram line (121).

Even though the difference was not statistically significant in late presenters, there was a trend to the SNAP regimen being inferior with adjusted odds ratio exceeding 1. We therefore cannot completely exclude the possibility of inferiority of the SNAP regimen in this sub-group. The unusually low rate of hepatotoxicity of 4% in the late-presenter group treated with the 21h regimen compared to published data in historical cohorts suggests that there is residual confounding from recording bias. This is supported by the finding of differential results in the outcomes of ALT peak>1000 between centres. In patients with delayed, this was significantly higher in the SNAP regimen in Edinburgh but not in Newcastle. This variation between the centres might be due to chance or due to the bias in data collection resulting from different treatment pathways. For instance, the Edinburgh data although including 720 patients with the standard regimen did not report any patients above the 300-nomogram band and may impact on the representativeness of the patient population included.

Given the sensitivity around paracetamol-induced hepatotoxicity in the UK leading to the MHRA recommending a lower nomogram line in the UK compared to other countries, any new regimen and protocol will need to be demonstrably non-inferior and the criteria for early discharge sufficiently robust to gain widespread acceptance. Our proposed 12h discharge criteria were derived from the UK nomogram line as a starting point, suggesting that patients at 16h with a paracetamol<12.5 mg/L and normal ALT do not require treatment. The risk of hepatotoxicity requiring liver unit admission and deaths without NAC treatment if the paracetamol concentration below the 100-nomogram line has been estimated to be less than 1 in 4400. Assuming that NAC treatment reduces the risk of hepatotoxicity by 90% or more in patients treated within 8-10 hours, early discharge after a 300mg/kg NAC dose with these same criteria is likely to be associated with a risk of less than 1 in 44000. This risk is likely to be reduced further by the addition of an additional safety net in our clinical decision rule: ALT doubling or more from admission even if still within the normal range. This is likely to detect most patients developing incipient hepatotoxicity. We therefore surmise that this 12h clinical decision rule is sufficiently safe to enable early discharge. The clinical risk associated with this change in practice is much lower than what is tolerated in other acute medical conditions where clinical decision rules are used to facilitate discharge e.g Blatchford score for upper GI bleeding, troponin I for risk stratification of acute coronary syndromes or D-dimer for venous thromboembolism.

The inclusion of the Australian 2-bag regimen using a similar 50 mg/kg/h loading regimen in the Australian and New Zealand guidelines support this approach. In November 2021, the Royal College of Emergency Medicine endorsed the use of the SNAP regimen as the standard of care in emergency departments. The protocol developed in this thesis is being considered by the National Poisons Information Service for inclusion on TOXBASE as the standard of care.

There remains some uncertainty over the applicability of the SNAP regimen in children where experience of its use is more limited. Children generally take lower doses of paracetamol in therapeutic excess or overdose and are considered at lower risk of hepatotoxicity compared to adults. A consensus expert opinion from relevant stakeholders such as paediatricians and paediatric clinical pharmacologists is required as obtaining direct evidence of efficacy in this group is difficult. The likely impact of the implementation of the SNAP regimen is a reduction in adverse reactions to

acetylcysteine, a reduction in errors associated with acetylcysteine and a reduction in the length of hospital stay.

6.4. Implications for patients, practice and future research

The present thesis has proven to be timely and important because it i) provides a novel, and short regimen , with less infusion adverse reaction and comparable efficacy to the standard regimen to help patients with paracetamol overdose to have short-term treatment and comparable outcomes at least for those with low risk group ; ii) will provide health care teams with a simpler regimen to be follow to better manage their patients with low risk of hepatotoxicity; and iii) can facilitate paracetamol overdose management in the NHS providing an effective clinical decision rule solution for the majority of cases of paracetamol overdose cases, which represent low risk. Thus, the studies in this thesis have the potential to impact on the health of those with paracetamol overdose, and on NHS resource use. There is a high level of interest currently amongst clinical care teams about how to effectively use the SNAP regimen in treatment patients with paracetamol poisoning. Results of the present study have informed development of an adequately powered clinical pathway for all low-risk group of paracetamol overdose using SNAP, which is currently implemented locally in UK for only those who had previous experience of NAARs. If the SNAP clinical pathway is to be confirmed, this will improve clinical practice, patient management and outcomes while leading to significant savings for the NHS, through reduction treatment failure and hospital admissions. Further research is needed to focus on those with high-risk group, and statistical tools to predict the hepatotoxicity for those who arrive late to the hospital and those with excessive overdose.

A prospective national audit of the SNAP protocol may provide information on whether these objectives are achieved and provide clarification on areas of uncertainty, for example, efficacy in late presenters. After over 4 decades of using a fixed 3-bag acetylcysteine regimen, there is still uncertainty about the optimal NAC regimen for different patient risk and patterns of overdose. This research has shown that it is possible to treat many low-risk patients with a shorter acetylcysteine regimen. The main barrier to discharging patients early is that the ALT does not rise sufficiently early in paracetamol-induced hepatotoxicity. New biomarkers being developed as point-of-care tests may in future allow for better risk stratification both at presentation and to tailor the NAC regimens according to risk.

Appendix A

1. North East Postgraduate Conference 2018, November 9, 2018 at Newcastle Civic Centre, UK.

Evaluation of a shorter 12h acetylcysteine regimen and development of a simpler acetylcysteine (SNAP) protocol for the treatment of paracetamol poisoning

AlRossies A, Potts A, Hill SL, Wood DM, Dargan PI, Thanacoody HKR, Thomas SHL

Introduction:

- Paracetamol overdose accounts for 42.5% of all hospital admissions with poisoning in the UK.
- N-acetylcysteine (NAC) is the antidote of choice for treatment of paracetamol overdose but the current 3-bag regimen is associated with adverse reactions and medication errors.
- A shorter 12h regimen has been shown to reduce adverse reactions.(1)

Objectives:

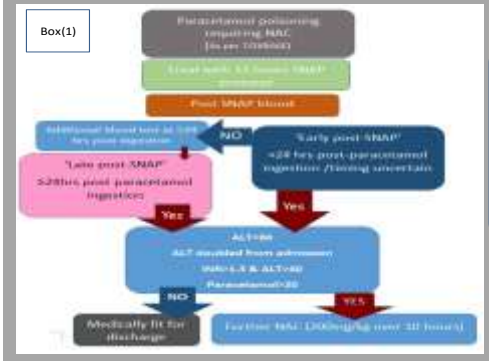
- To evaluate effectiveness of a shorter 12-hour acetylcysteine regimen for treatment of paracetamol overdose.
- To develop criteria to allow safe early discharge of selected patients soon after use of the SNAP regimen.

	UK-approved regimen (3-bag)	SNAP regimen (2-bag)
Duration	21 hours	12 hours
Loading dose	150mg/kg Infuse over 1 hour	100mg/kg Infuse over 2 hours
Maintenance dose	50mg/kg Infuse over 4 hours	200 mg/kg Infuse over 10 hours
	100mg/kg Infuse over 16 hours	

Methods:

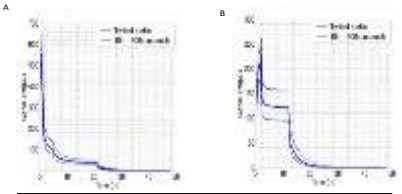
- Pharmacokinetic simulation of acetylcysteine concentrations using different regimens was performed using A4S software to select the most pragmatic intravenous acetylcysteine regimen for clinical use.
- A clinical protocol using this modified SNAP regimen (box1) was implemented in routine clinical practice in St Thomas Hospital, London and Royal Victoria Infirmary, Newcastle in October 2016 after local approvals to treat all patients requiring NAC for paracetamol overdose.
- Data on efficacy outcomes (peak ALT and peak INR) was collected prospectively until 31st August 2018 and compared to data from audits of patients treated with the conventional 21h regimen prior to October 2016.
- We used the clinical data to derive a simplified SNAP protocol (box2) for routine clinical use.

Box(1)



Results:

Pharmacokinetics Simulation:



Expected Acetylcysteine Concentration.		
Regimen	Peak Conc.	Steady-state Conc.
A. Conventional	560mg/l	40mg/l
B. SNAP	220mg/l	120mg/l

Outcomes of SNAP and conventional NAC regimens:

Outcomes	SNAP (1015)	Conventional (413)	Absolute difference (95% CI)	P-value
NAC>300 mg/kg [N (%)]	128/1015 (12.6)	47/413 (11.4)	1.2 (-2.7 , 4.7)	0.53
Peak ALT>1000 [N (%)]	40/1013 (3.9)	14/411 (3.4)	0.5 (-1.9 , 2.4)	0.65
Peak INR>2 [N (%)]	36/1005 (3.5)	9/409 (2.2)	1.3 (-0.9 , 3.0)	0.2
Anti-histamine treatment [N (%)]	32/1015 (3.2)	36/411 (8.7)	-5.5 (-2.8 , -8.8)	0.0

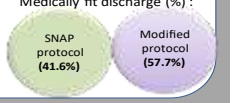
Simple clinical decision rule:

Box(2)

CONTINUE NAC treatment:
- ✓ Paracetamol >20 mg/L
- ✓ ALT 41-80 IU/L & doubled from admission
- ✓ ALT >80 IU/L.

DISCONTINUE NAC treatment:
- ✓ Paracetamol <10 mg/L
- ✓ ALT ≤40 IU/L
- ✓ ALT not doubled from admission
- ✓ INR <1.5

Medically fit discharge (%) :



Conclusion:

A simpler and shorter acetylcysteine regimen appears to be clinically effective.
The criteria for treatment continuation and discontinuation require validation in larger cohorts of patients.

Reference:
1. Bateman DN, Dear JW, Thanacoody HKR et al. Reduction of adverse effects from intravenous acetylcysteine treatment for paracetamol poisoning: a randomized controlled trial. *Lancet* 2014; 383(9918):697-704.

2. British Pharmacology Society Meeting 2018, December 20, 2018 at the Queen Elizabeth II Conference Centre, London.

Efficacy of a shorter 12h intravenous acetylcysteine (SNAP) regimen following single acute paracetamol overdose

Amani S Alrossies [1],Ruben HK Thanacoody [1,2],James Harnett[3],Kerry Layne[3],John RH Archer[3],Simon L Hill [1,2],David M Wood[3,4],Paul I Dargan[3,4],Simon HL Thomas [1,2]
(1)Newcastle University, Newcastle upon Tyne, United Kingdom; (2)Newcastle Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom ;(3)Guy's & St Thomas NHS Foundation Trust, London, United Kingdom;(4)Faculty of Life Sciences and Medicine, King's College London, London, UK

Introduction :

- Paracetamol overdose accounts for 42.5 % of all hospital admissions with poisoning in the UK.
- Acetylcysteine (NAC) is the antidote of choice for treatment of paracetamol overdose but the current UK -approved 3 -bag regimen is associated with adverse reactions and medication errors.
- A modified 2 -bag 12h acetylcysteine (NAC) regimen ("SNAP") causes fewer adverse reactions, is simpler and quicker to administer than the current 3 -bag 21h NAC regimen. [1]
- This research was performed to compare the clinical effectiveness of the SNAP regimen compared to the current regimen.

Methodology:

- The modified 12h 'SNAP' regimen (Fig 1) was introduced in 2016 in Royal Victoria Infirmary (RVI) and St Thomas Hospital (STH), London to treat all patients requiring NAC for paracetamol overdose using a protocol approved by local medicines management committees (Fig 2).
- Routine clinical data was collected prospectively from 1st June 2016 to 31st August 2018 in STH and 1st October 2016 to 30th November 2018 in RVI.

Figure 1

	UK-approved regimen (3-bag)	SNAP regimen (2-bag)
Duration	21 hours	12 hours
Loading dose	150mg/kg Infuse over 1 hour	100mg/kg Infuse over 2 hours
Maintenance dose	50mg/kg Infuse over 4 hours	200 mg/kg Infuse over 10 hours
	100mg/kg Infuse over 16 hours	

Figure 2

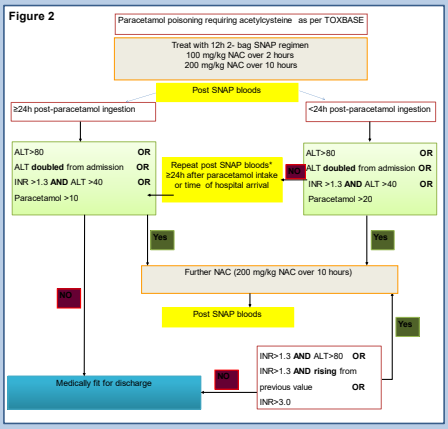
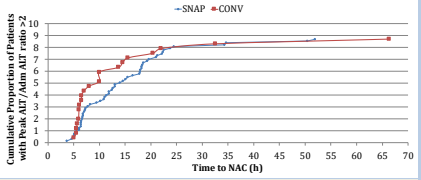
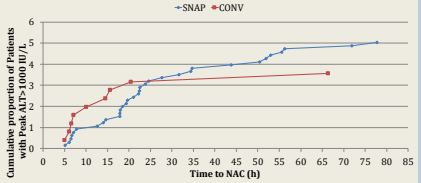


Figure 3 Cumulative Proportion of Acute Single Overdose Patients with Peak ALT/Admission ALT ratio>2 vs Time to NAC



Cumulative Proportion of Acute Single Overdose Patients with Peak ALT>1000 vs Time to NAC



Results:

- Data was available in 515 acute single paracetamol overdose patients treated with NAC within 8 hours of ingestion and in 341 patients treated more than 8 hours post-ingestion.
- In patients treated within 8 hours post -ingestion, the median peak ALT was significant lower in patients treated with the SNAP regimen compared to 21h regimen (19 vs 22.5, p=0.048) but there was no difference in the median peak ALT/admission ALT ratio or the median peak INR.(Table 1)
- In patients treated more than 8 hours post -ingestion, there was no difference in peak ALT, peak ALT/admission ALT ratio or peak INR between the two regimens. (Table 1)
- A peak ALT which was more than double the admission ALT occurred in 61/621 (9.8%) with the SNAP regimen and 23/250(9.2%) with the conventional regimen (Figure 3)
- 33/619 (5.3%) of these patients developed a peak ALT>1000 with the SNAP regimen and 9/237(3.8%) with the conventional regimen. (Figure 3)

Table 1 All Acute single paracetamol overdoses

	Time to NAC<8 (h) [n=515]		P-value	Time to NAC≥8 (h) [n=341]		P-value
	Conventional [n=140]	SNAP [n=375]		Conventional [n=97]	SNAP [n=244]	
Peak ALT [median,(IQR)]	22.5(23)	19(14)	0.048	25(41)	24(48)	0.48
Peak INR [median,(IQR)]	1.2(0.2)	1.2(0.2)	0.9	1.2(0.2)	1.2(0.3)	0.08
Peak ALT/Adm ALT [median,(IQR)]	1(0.1)	1(0.07)	0.52	1(0.2)	1.2(0.3)	0.92
Peak INR/Adm INR[median,(IQR)]	1.1(0.11)	1.2(0.12)	0.29	1.1(0.2)	1.18(0.18)	0.001
Peak ALT>1000 [no.(%)]	4(2.9)	6(1.6)	0.34	5(5.2)	27(11.1)	0.093

Conclusions:

- A simpler 12h SNAP regimen appears to be similar effective in patients treated within 8 hours of overdose.
- More data is required to establish efficacy in patients treated later than 8 hours after a paracetamol overdose before wider implementation into clinical practice .

Reference:

1. Bateman DN, Dear JW, Thanacoody HKR et al. Reduction of adverse effects from intravenous acetylcysteine treatment for paracetamol poisoning: a randomized con trolled trial. *Lancet* 2014; 383(9918): 697-704.

3. British Pharmacology Society Meeting 2019, December 19, 2019 at Cromdale Hall, Edinburgh International Conference Centre, UK.

Derivation of a clinical decision rule for early discharge of patients with paracetamol poisoning treated with a shorter 12-hour acetylcysteine (SNAP) regimen

Amani S Alrossies [1], Ruben HK Thanacoody [2,3], James Harnett [4], Kerry Layne [4], John RH Archer [4], Simon L Hill [2,3], David M Wood [4,5], Paul I Dargan [4,5], Simon HL Thomas [2,3]
(1) Princess Nourah bint Abdulrahman University/College of Pharmacy, Riyadh, Saudi Arabia; (2)Newcastle University, Newcastle upon Tyne, United Kingdom; (3)Newcastle Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom ;(4)Guy's & St Thomas NHS Foundation Trust, London, United Kingdom; (5)Faculty of Life Sciences and Medicine, King's College London, London, UK

Introduction:

- Paracetamol overdose accounts for 42.5% of all hospital admissions with poisoning in the UK.
- Acetylcysteine (NAC) is the antidote of choice for treatment of paracetamol overdose but the current UK -approved 3 -bag regimen i s associated with adverse reactions and medication errors.
- A modified 2 -bag 12h acetylcysteine (NAC) regimen ('SNAP') causes fewer adverse reactions and is simpler and quicker to administer than the current 3 -bag 21h NAC regimen. [1]
- This research was performed to develop criteria to allow safe early discharge of selected patients after use of the 12h SNAP regimen.

Methodology:

- The modified 12h 'SNAP' regimen was introduced in 2016 in Royal Victoria Infirmary (RVI) and St Thomas Hospital (STH), London to treat all patients requiring NAC for paracetamol overdose using a protocol approved by local Medicines Management Committees (Fig 1).
- Routine clinical data was collected prospectively from 1 st June 2016 to 31 st August 2018 at STH and 1 st October 2016 to 30th November 2018 at the RVI.
- In patients in whom there were paired "early" (12h post -infusion) and "late" (24h post -overdose) samples, we modelled clinical rules using different cut -offs of ALT, INR and paracetamol concentration iteratively to derive criteria that accurately identified patients who did or did not require further treatment after the 12h SNAP NAC infusion and those who require additional blood testing before discharge.

Table 1 Outcome after different discharge criteria at 12 hours

Model	Suggested criteria for discharge	% meeting suggested discharge criteria at 12 hours	% meeting current discharge criteria at 24 hours post overdose
1	Paracetamol<20mg/L , ALT<2xULN, ALT<2x admission ALT at admission and INR<1.4	57.7	47.1
2	Paracetamol<5mg/L , ALT<ULN, ALT <2x admission ALT and INR<1.5	53.2	46.4
3	Paracetamol<5mg/L , ALT<ULN, ALT ≤2x admission ALT and INR<1.4	52.5	46.4
4	Paracetamol<20mg/L , ALT<ULN, ALT <2x admission ALT and INR≤1.5	58.5	52.1
5	Paracetamol<10mg/L , ALT≤ULN, ALT <2x admission ALT and INR<1.5	56.1	52.6

Figure 1

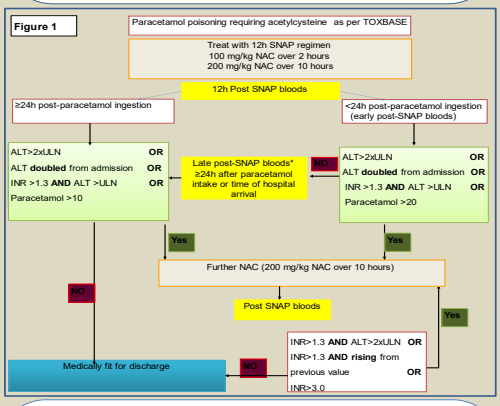
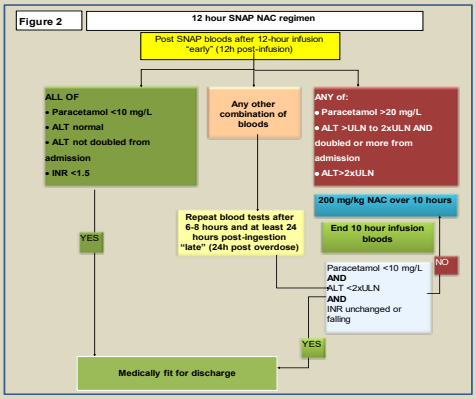


Table 2 Outcome after different criteria for continuing NAC treatment

Model	Suggested continuing treatment criteria	% continuing treatment at 12 hours	% observed and repeat blood test at 24h post-overdose
1	Paracetamol≥20mg/L or ALT>2xULN or ALT ≥2x admission ALT or INR≥1.4	24.9	17.4
2	Paracetamol>20mg/L or ALT>2xULN or (ALT 40-80 AND INR≥1.5)	13.6	33.2
3	Paracetamol>10mg/L or ALT>2xULN or ALT ≥2 x admission ALTor INR≥1.4	26.7	20.8
4	Paracetamol>20mg/L or (ALT>ULN AND INR>1.5) or ALT>100	12.6	28.9
5	Paracetamol>20mg/L or (ALT>ULN to 2xULN AND ALT >2 x admission ALT) or ALT>2xULN	14	29.9

Figure 2



Results

- 1088 patients were treated with the SNAP regimen during the study period.
- Paired 12h and 24h blood results were available in 420 patients.
- 221/420 (52.6%) of these patients met all of the following criteria on the "early" (12h post -infusion) blood samples: ALT≤ULN; paracetamol concentration<10 mg/L; ALT not doubled from admission; INR<1.5 (model 5, Table 1).
- None of these patients required re -institution of NAC treatment following "late" (24h post -overdose) blood samples.
- These potential criteria for discharge were met in 610/1088 (56%) of all patients treated with the SNAP regimen at the end of the 12h infusion.
- Predicted outcomes for different criteria are shown in Tables 1 and 2. These were used to construct a simplified SNAP protocol (Fig 2).

Conclusion:

- A simple clinical decision rule may accurately identify low -risk patients who can be discharged safely after the shorter 12h SNAP regimen. This requires validation in larger cohorts of patients before implementation into routine clinical practice.

Reference:
1. Bateman DN, Dear JW, Thanacoody HKR et al. Reduction of adverse effects from intravenous acetylcysteine treatment for paracetamol poisoning: a randomized con trolled trial. *Lancet* 2014; 383(9918): 697-704.

4. 39th International Congress of the European Association of Poisons Centres and Clinical Toxicologists, May 24, 2019, Napoli, Italy.

Derivation of a clinical decision rule for early discharge of patients with paracetamol poisoning treated with a shorter 12-hour acetylcysteine (SNAP) regimen

Alrossies AS
Lecturer in Pharmacy at PNU
PhD student at Newcastle University

Ruben HK Thanacoody, James Harnett, Kerry Layne, John RH Archer, Simon L Hill, David M Wood, Paul I Dargan, Simon HL Thomas

NHS Guy's and St Thomas' NHS Foundation Trust

Newcastle University

The Newcastle upon Tyne Hospitals NHS NHS Foundation Trust

5. British Pharmacology Society Meeting 2019, December 19, 2019 at Cromdale Hall, Edinburgh International Conference Centre, UK.

Efficacy of a shorter 12h intravenous acetylcysteine (SNAP) regimen following single acute paracetamol overdose stratified by risk of paracetamol-induced hepatotoxicity.

Alrossies AS[1,5], James Harnett[3], John RH Archer[3], Simon L Hill[1,2], David M Wood[3,4], Paul I Dargan[3,4], Simon HL Thomas[1,2], Ruben HK Thanacoody[1,2]

(1)Newcastle University, Newcastle upon Tyne, United Kingdom (2)Newcastle Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom (3)Guy's & St Thomas NHS Foundation Trust, London, United Kingdom (4)Faculty of Life Sciences and Medicine, King's College London, London, UK (5) Princess Nourah bint Abdulrahman University

Introduction

- Paracetamol is the most common drug overdose reported to poison centres (Brass et al., 2018).
- Paracetamol overdose accounts for 42.5% of all hospital admissions with poisoning in the UK.
- N-acetylcysteine (NAC) is the antidote of choice for treatment of paracetamol overdose but the current 3-bag 20.25 h acetylcysteine (NAC) regimen is associated with a high risk of anaphylactoid reactions.
- A modified 2-bag 12h acetylcysteine (NAC) regimen ('SNAP') causes fewer adverse reactions, is simpler and quicker to administer than the current 3-bag 21h NAC regimen.

Objective

To compare the efficacy of a 2-bag 12h acetylcysteine (NAC) regimen ('SNAP') in hepatotoxicity prevention to the current 3-bag 21h NAC regimen in patients with acute paracetamol poisoning.

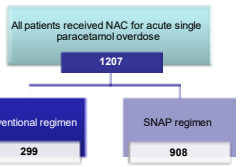
Methods

- The 'SNAP' regimen was introduced in 2016 locally to treat all patients requiring NAC for paracetamol overdose. Data on efficacy outcomes (peak ALT and peak INR) was collected prospectively until August 2019 and compared to data from audits of patients treated with the conventional regimen prior to October 2016.

Acetylcysteine (NAC) treatment regimen		
	CConventional regimen (3-bag)	SNAP regimen (2-bag)
Duration	21 hours	12 hours
Loading	150mg/kg Infuse over 1 hour	100mg/kg Infuse over 2 hours
Maintenance dose	50mg/kg Infuse over 4 hours	200 mg/kg Infuse over 10 hours
	100mg/kg Infuse over 16 hours	

- All acute overdoses patients were categorised into 4 groups using 2 established risk factors for developing hepatotoxicity (**ALT>1000 or INR>2**): paracetamol concentration band and time from ingestion to start acetylcysteine.

Results



Outcomes of current & SNAP regimen of ALT>1000 after starting NAC

	Peak ALT≥1000		Absolute difference (95% CI)
Type of risk	Conventional	SNAP	
NAC started≤12 and Nomogram band ≤150 [N (%)]	0/107(0)	0/372(0)	0 (-1.2-3.4)
NAC started≤12 and Nomogram band >150 [N (%)]	5/115(4.3)	8/307(2.6)	-1.7 (-1.7 – 7.3)
NAC started>12 and Nomogram band ≤150 [N (%)]	1/29(3.4)	2/72(2.7)	-0.7 (-6.6 – 14.5)
NAC started>12 and Nomogram band >150 [N (%)]	5/31(16.1)	11/87(12.6)	-3.6 (-8.9 – 20.9)

Outcomes of current & SNAP regimen of INR>2 after starting NAC

	Peak INR≥2		Absolute difference (95% CI)
Type of risk	Conventional	SNAP	
NAC started≤12 and Nomogram band ≤150 [N (%)]	0/107(0)	2/372(0.5)	0.5 (-2.9 – 1.8)
NAC started≤12 and Nomogram band >150[N (%)]	3/115(2.6)	8/307(2.6)	0 (-2.9 – 4.9)
NAC started>12 and Nomogram band ≤150 [N (%)]	1/29(3.4)	0/72(0)	3.4 (-2.4 – 17.1)
NAC started>12 and Nomogram band >150[N (%)]	2/31(6.5)	9/87(10.3)	3.8 (-11. – 13.2)

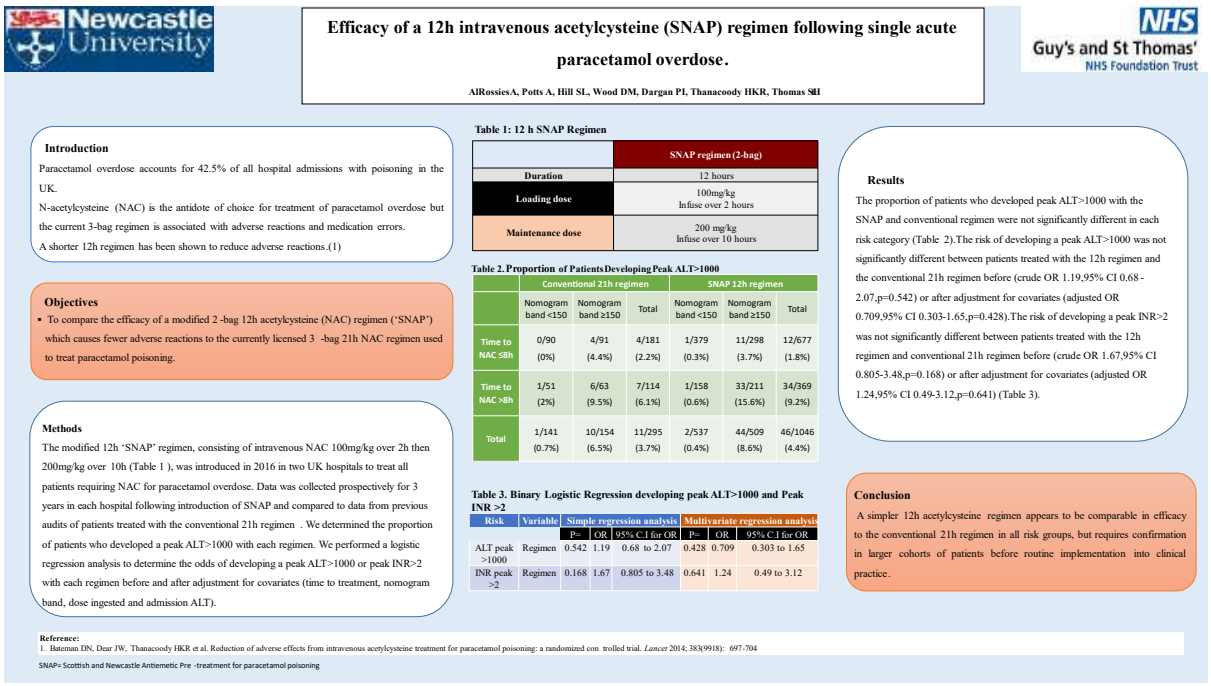
Conclusions

Both regimens appear to be comparable in efficacy in all 4 risk groups, but a larger cohorts of patients is required before clinically implementation .

References

- Bateman DN, Dear JW, Thanacoody HKR et al. Reduction of adverse effects from intravenous acetylcysteine treatment for paracetamol poisoning: a randomized controlled trial. *Lancet* 2014; 383(9918): 697-704.
- Pettie JM, Caparrotta TM, Hunter RW et al. Safety and Efficacy of the SNAP 12 -hour Acetylcysteine Regimen for the Treatment of Paracetamol Overdose. EClinicalMedicine . 2019; 11:11-17.

6. 41st International Congress of the European Association of Poisons Centres and Clinical Toxicologists, May 27, 2021. Virtual Congress platform.



Efficacy of a 12h intravenous acetylcysteine (SNAP) regimen following single acute paracetamol overdose.

AlRossiesA, Potts A, Hill SL, Wood DM, Dargan PI, Thanacoody HKR, Thomas SH

Newcastle University

Guy's and St Thomas' NHS Foundation Trust

Introduction

Paracetamol overdose accounts for 42.5% of all hospital admissions with poisoning in the UK.

N-acetylcysteine (NAC) is the antidote of choice for treatment of paracetamol overdose but the current 3-bag regimen is associated with adverse reactions and medication errors.

A shorter 12h regimen has been shown to reduce adverse reactions.(1)

Objectives

- To compare the efficacy of a modified 2-bag 12h acetylcysteine (NAC) regimen ('SNAP') which causes fewer adverse reactions to the currently licensed 3 -bag 21h NAC regimen used to treat paracetamol poisoning.

Methods

The modified 12h 'SNAP' regimen, consisting of intravenous NAC 100mg/kg over 2h then 200mg/kg over 10h (Table 1), was introduced in 2016 in two UK hospitals to treat all patients requiring NAC for paracetamol overdose. Data was collected prospectively for 3 years in each hospital following introduction of SNAP and compared to data from previous audits of patients treated with the conventional 21h regimen . We determined the proportion of patients who developed a peak ALT>1000 with each regimen. We performed a logistic regression analysis to determine the odds of developing a peak ALT>1000 or peak INR>2 with each regimen before and after adjustment for covariates (time to treatment, nomogram band, dose ingested and admission ALT).

Table 1: 12 h SNAP Regimen

	SNAP regimen (2-bag)
Duration	12 hours
Loading dose	100mg/kg Infuse over 2 hours
Maintenance dose	200 mg/kg Infuse over 10 hours

Table 2. Proportion of Patients Developing Peak ALT>1000

	Conventional 21h regimen			SNAP 12h regimen		
	Nomogram band <150	Nomogram band ≥150	Total	Nomogram band <150	Nomogram band ≥150	Total
Time to NAC ≤8h	0/90 (0%)	4/91 (4.4%)	4/181 (2.2%)	1/379 (0.3%)	11/298 (3.7%)	12/677 (1.8%)
Time to NAC >8h	1/51 (2%)	6/63 (9.5%)	7/114 (6.1%)	1/158 (0.6%)	33/211 (15.6%)	34/369 (9.2%)
Total	1/141 (0.7%)	10/154 (6.5%)	11/295 (3.7%)	2/537 (0.4%)	44/509 (8.6%)	46/1046 (4.4%)

Table 3. Binary Logistic Regression developing peak ALT>1000 and Peak INR >2

Risk	Variable	Simple regression analysis			Multivariate regression analysis		
		P=	OR	95% C.I for OR	P=	OR	95% C.I for OR
ALT peak >1000	Regimen	0.542	1.19	0.68 to 2.07	0.428	0.709	0.303 to 1.65
INR peak >2	Regimen	0.168	1.67	0.805 to 3.48	0.641	1.24	0.49 to 3.12

Results

The proportion of patients who developed peak ALT>1000 with the SNAP and conventional regimen were not significantly different in each risk category (Table 2).The risk of developing a peak ALT>1000 was not significantly different between patients treated with the 12h regimen and the conventional 21h regimen before (crude OR 1.19,95% CI 0.68 - 2.07,p=0.542) or after adjustment for covariates (adjusted OR 0.709,95% CI 0.303-1.65,p=0.428).The risk of developing a peak INR>2 was not significantly different between patients treated with the 12h regimen and conventional 21h regimen before (crude OR 1.67,95% CI 0.805-3.48,p=0.168) or after adjustment for covariates (adjusted OR 1.24,95% CI 0.49-3.12,p=0.641) (Table 3).

Conclusion

A simpler 12h acetylcysteine regimen appears to be comparable in efficacy to the conventional 21h regimen in all risk groups, but requires confirmation in larger cohorts of patients before routine implementation into clinical practice.

Reference:
1. Bateman DN, Dear JW, Thanacoody HKR et al. Reduction of adverse effects from intravenous acetylcysteine treatment for paracetamol poisoning: a randomized con trolled trial. *Lancet* 2014; 383(9918): 697-704

SNAP= Scottish and Newcastle Antiemetic Pre -treatment for paracetamol poisoning

Objective: To assess the risk factors for esophageal stricture a late complication of alkali ingestion in children.
Methods: A retrospective analysis of medical records of all patients admitted after strong alkali ingestion to a pediatric poisoning center, over a four year period. Data collected were: clinical features during the acute period and esophageal findings revealed by the upper digestive endoscopy. Statistical testing was performed using the chi-squared test or Mann-Whitney U Test, and P-values lower than 0.05 were considered as statistically significant.
Results: A total of 72 children aged 1-18 years with strong alkali ingestion were admitted in our center between April 2015 and August 2019. According to the di Constanzo classification [1] the following findings were revealed by the initial endoscopy performed in the first 72 hours: zero degree injury in 24 patients (66%), first degree in 18 (25%), second degree in 22 (30%), and third degree in 8 (11%). The second endoscopy was performed between day 21 and day 28 after ingestion and detected esophageal stricture in 8 patients (11%). All the 8 patients presented severe symptomatology during the acute period (vomiting, gastrointestinal bleeding or acute respiratory failure), but only gastrointestinal bleeding could be statistically correlated with the presence of esophageal stricture ($p = 0.04$). There was a statistical correlation between the degree of initial esophageal injury and the development of the esophageal stricture ($p = 0.011$) [2] as follows: 5 cases with third degree lesions, 1 with second degree lesions and 2 with first degree lesions. The therapeutic approach in patients with caustic esophageal stricture included repeated esophageal dilatation in 5 children and gastrostomy pending esophagoplasty in 2 cases. One patient did not return for the scheduled follow-up.
Conclusion: In this study the presence of esophageal stricture could be correlated with the severity of the initial esophageal lesion [2], and most cases involved had second and third degree lesions. Gastrointestinal bleeding during the acute phase represents a risk factor for the development of the esophageal stricture, but further studies are necessary to confirm this hypothesis as the main limitation of the study was the rather small number of cases.

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200. Efficacy of a 12h intravenous acetylcysteine (SNAP) regimen following single acute paracetamol overdose

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Objective: To compare the efficacy of a modified 2-bag 12h acetylcysteine (NAC) regimen ("SNAP") which causes fewer adverse reactions to the currently licensed 3-bag 21h NAC regimen used to treat paracetamol poisoning [1].
Methods: The modified 12h "SNAP" regimen (intravenous NAC 100 mg/kg over 2h then 200 mg/kg over 10 h), was introduced in 2016 in two UK hospitals to treat all patients requiring NAC for paracetamol overdose. Data was collected prospectively for 3 years after "SNAP" introduction in each hospital and compared to data from previous audits of patients treated with the conventional 21h regimen. We determined the proportion of patients who developed a peak ALT >1000 with each regimen. We performed a logistic regression analysis to determine the odds of developing a peak ALT >1000 or peak INR >2 with each regimen before and after adjustment for covariates (time to treatment, nomogram band, dose ingested and admission ALT).
Results: The proportion of patients who developed peak ALT >1000 with the SNAP and conventional regimen were not significantly different in each risk category (Table 1). The risk of developing a peak ALT >1000 was not significantly different between patients treated with the 12h regimen and the conventional 21h regimen before (crude OR 0.810, 95% CI 0.39-1.68, $p = 0.572$) or after adjustment for covariates (adjusted OR 0.692, 95% CI 0.32-1.51, $p = 0.354$). The risk of developing a peak INR >2 was not significantly different between the two groups (crude OR 1.24, 95% CI 0.49-3.13, $p = 0.65$) or after adjustment for covariates (adjusted OR 1.04, 95% CI 0.39-2.72, $p = 0.94$).
Conclusion: A simpler 12h acetylcysteine regimen appears to be comparable in efficacy to the conventional 21h regimen in all risk groups, but requires confirmation in larger cohorts of patients before routine implementation into clinical practice.

Reference

[1] Bateman DN, Dear JW, Thanacoody HKR, et al. Reduction of adverse effects from intravenous acetylcysteine treatment for paracetamol poisoning: a randomized controlled trial. Lancet. 2014;383:697–704.

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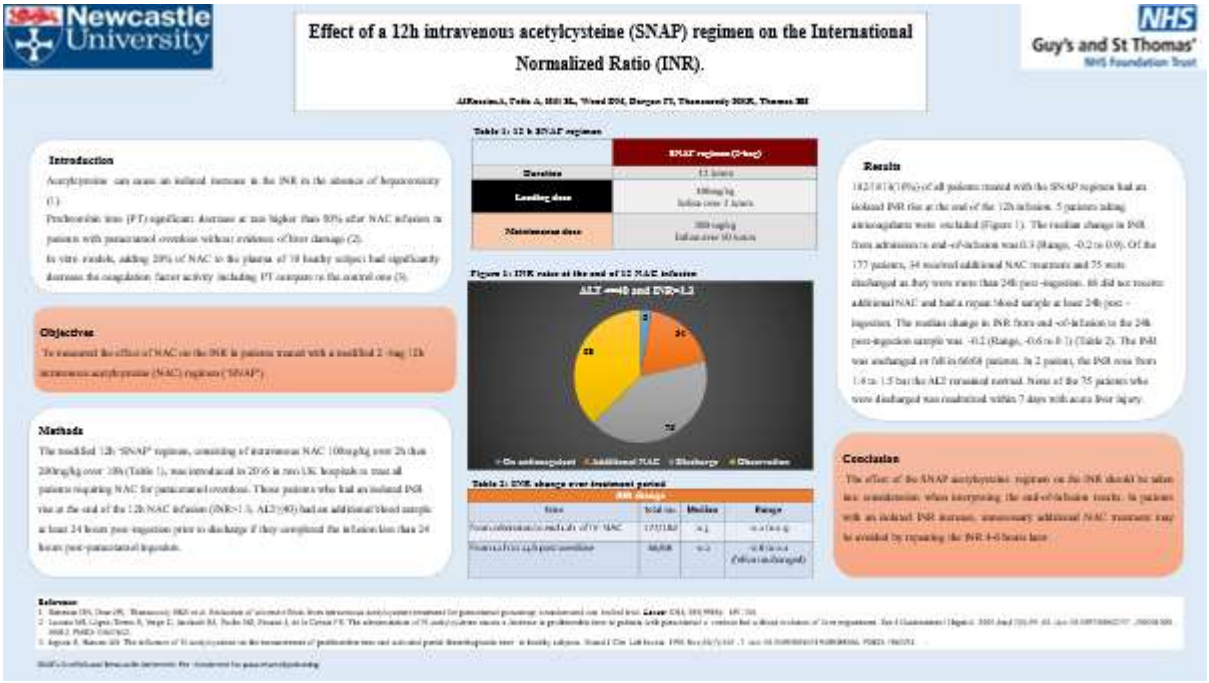

590 EAPCCT 2021 ABSTRACTS

398. Effect of a 12-hour intravenous acetylcysteine (SNAP) regimen on the International Normalized Ratio (INR)

Amani S. Alrossies[a], David Wood[b], Paul I. Dargan[c], Simon H. L. Thomas[d] and Ruben H. K. Thanacoody[a]

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Objective: Acetylcysteine can cause an isolated increase in the INR in the absence of paracetamol-induced hepatotoxicity [1]. We measured the effect of NAC on the INR in patients treated with a modified 2-bag 12-hour intravenous acetylcysteine (NAC) regimen ("SNAP").

Methods: The modified 12-hour "SNAP" regimen, consisting of intravenous NAC 100 mg/Kg over 2 hours, then 200 mg/Kg over 10 hours, was introduced in 2016 in two UK hospitals to treat all patients requiring NAC for paracetamol overdose. Those patients who had an isolated INR rise at the end of the 12-hour NAC infusion (INR >1.3, ALT ≤40) had an additional blood sample at least 24 hours post-ingestion prior to discharge if they completed the infusion less than 24 hours post-paracetamol ingestion.

Results: Overall 182/1813 (10%) of all patients treated with the SNAP regimen had an isolated INR rise at the end of the 12-hour infusion. Five patients taking anticoagulants were excluded. The median change in INR from admission to end-of-infusion was 0.3 [range −0.2 to 0.9). Of the remaining 177 patients, 34 received additional NAC treatment and 75 were discharged as they were more than 24 hours post-ingestion. None of the 75 patients who were discharged was readmitted within 7 days with acute liver injury; 68 patients did not receive additional NAC and had a repeat blood sample at least 24 hours post-ingestion. The median change in INR from end-of-infusion to the 24 hour post-ingestion sample was −0.2 (range −0.6 to 0.1). The INR was unchanged or decreased in 66/68 patients and increased from 1.4 to 1.5 in 2 patients. In all 68 patients, the ALT remained normal.

Conclusion: The effect of the SNAP acetylcysteine regimen on the INR should be taken into consideration when interpreting the end-of-infusion results. In patients with an isolated INR increase, unnecessary additional NAC treatment may be avoided by repeating the INR 4-6 hours later.

Reference

[1] Schmidt LE, Knudsen TT, Dalhoff K, et al. Effect of acetylcysteine on prothrombin index in paracetamol poisoning without hepatocellular injury. Lancet. 2002;360:1151–2.

8. The British Toxicology Society Annual Congress 2022, April 5th 2022, Hilton Newcastle Gateshead, UK.

Efficacy of a 12h intravenous acetylcysteine (SNAP) regimen in patients at high risk of hepatotoxicity following single acute paracetamol overdose.

Newcastle University

Amani Alrossies

Lecturer in Pharmacy at PNU

PhD student at Newcastle University

Appendix B

The Newcastle Hospitals NHS

Management of Paracetamol Overdose
in adults and children over 6 years old
SNAP 12-hour regimen

MRN:
Name:
DOB:
Address:

1 Initial Evaluation

Date of **presentation**: ___/___/___
Time at presentation: ___:___
Date of **last ingestion**: ___/___/___
Time at last ingestion: ___:___
Time since last ingestion: _____ hours
tick one:
☐ <8h ☐ 8-24h ☐ >24h ☐ Unknown

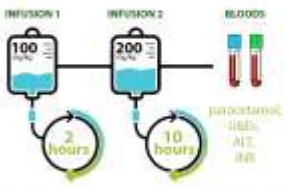
Total **overdose**: _____ **g**
Patient **weight**: _____ **kg** (use pre-pregnancy weight if pregnant & max. weight as 110kg)
Overdose **per weight**: _____ **mg/kg**

Pattern of ingestion (*tick one if known*):
☐ Single acute overdose (≥75mg/kg over a period 1 hour or less)
☐ Staggered overdose (≥75mg/kg over more than 1 hour **AND** deliberate self-harm)
☐ Therapeutic excess (≥75mg/kg over 24 hours **OR** >4 g each day over 2 days)

2 Management			Sign	Date/Time
A	Activated charcoal	Adult dose: 50g; Children dose: 1g/kg		
	Consider if **all**:	**Airway** is protected		
		Presents within **1 hour**		
		Overdose **>150 mg/kg**		
B	Blood tests	U&Es, LFTs, INR, paracetamol concentration		
	Take **at least 4 hours** from time of last ingestion. Record these in 'admission' bloods in the Blood Test Results Table overleaf.			
C	Acetylcysteine	See Dosing Table on page 3		
i	Start acetylcysteine **immediately** on admission if **any**:	Single acute overdose >150mg/kg & last ingestion **8-24 hours** ago		
		Single acute overdose >150mg/kg & **unknown** time of ingestion		
		Staggered overdose		
		Clinical features of **liver toxicity** (e.g., jaundice, liver tenderness)		
ii	Stop acetylcysteine **after admission blood** results if **all**:	**Paracetamol** concentration < 10mg/L or below the treatment line on the nomogram		
		ALT is normal (≤ 40IU/L)		
		INR is normal (≤ 1.3)		
		Patient is **asymptomatic**		

Paracetamol nomogram

SNAP 12-hour acetylcysteine protocol



iii	Start acetylcysteine **after admission blood** results if **any**:	**Paracetamol** concentration above the **nomogram** treatment line or greater than **10mg/L if therapeutic excess** overdose pattern		
		ALT > 40IU/L (consider specialist advice if chronically elevated)		
		INR > 1.3 (consider specialist advice if chronically elevated)		

The Newcastle Hospitals NHS

D	Drug reactions	Recognise: nausea, vomiting, flushing, urticarial rash, angioedema, tachycardia, wheeze.					
Consider taking the following actions:		☐ Temporarily **stop** the acetylcysteine infusion					
		☐ IV **chlorphenamine** 10 mg					
		☐ Restart the acetylcysteine infusion at a **slower** rate					
E	End of 2nd infusion	At 12 hours, take bloods for paracetamol concentration, U&Es, LFTs, INR.					
Continue acetylcysteine * if ***any*** :		Raised ALT (>40IU/L)	**OR**	INR>1.3 and ALT doubled or more from admission	**OR**	Paracetamol concentration greater than 10mg/L	
Medically fit for discharge if ***both*** :		Does not meet criteria above		**&**		Asymptomatic	

* **Extended acetylcysteine treatment**

- Any additional infusion bags of acetylcysteine should be administered at the **same dose (200 mg/kg) and infusion rate** as the 2nd infusion (see dosing table on page 3).
- **Take bloods** at the end of additional infusion bags for U&Es, LFTs, INR, and paracetamol concentration.
- **Start a 4th infusion bag** if the bloods taken at the end of 3rd infusion bag blood are abnormal, i.e., **any of**:
  a) ALT > 80 IU/L,
  b) ALT > 40 IU/L **AND** doubled or more from admission,
  c) ALT > 40 IU/L **AND** INR>1.3 and rising from previous value,
  d) Paracetamol concentration >10 mg/L.
- **Stop subsequent infusion bags** (i.e., 5th bag or more) if blood results are normalising, i.e., **either**:
  a) INR ≤1.3, **OR**
  b) INR < 3.0 and falling on consecutive blood tests.

Acetylcysteine Blood Test Results

Bloods	Baseline if available	Admission	End 2nd bag (12 h)	End 3rd bag	End 4th bag
Date/time					
Paracetamol conc. (mg/L)					
ALT (IU/L)					
INR					
Urea (mmol/L)					
Creatinine (μmol/L)					

See **Trust Guidelines** for detailed management of paracetamol overdose.

Specialist treatment

Consider haemodialysis if massive overdose (e.g., paracetamol conc. > 700 mg/L).

Consider urgent hepatology referral if metabolic acidosis or rapidly rising INR.

See **TOXBASE** for full guidelines

NPIS : 0344 892 0111

Document completed by:					
Date	Time	Name	Role/Grade	Bleep/Ext.	Signature

SNAP	Acetylcysteine Dosing Table Adults and children over 6 years.			
	First Infusion		**Second (and additional) Infusions**	
Infusion **fluid**	200 mL 5% glucose or 0.9% sodium chloride		1000 mL 5% glucose or 0.9% sodium chloride	
Infusion **duration**	2 hours		10 hours	
Acetylcysteine dose	**100 mg/kg**		**200 mg/kg**	
Patient **Weight** (kg)	Acetylcysteine **volume** (mL)	Infusion **Rate** (mL/h)	Acetylcysteine **volume** (mL)	Infusion **Rate** (mL/h)
40-49	23	100	45	100
50-59	28	100	55	100
60-69	33	100	65	100
70-79	38	100	75	100
80-89	43	100	85	100
90-99	48	100	95	100
100-109	53	100	105	100
≥110	55	100	110	100

ampoule = **200 mg/mL** acetylcysteine

NOTE: To ensure same infusion rate of 100 mL/hour for all weight bands, the same volume of 5% glucose as the acetylcysteine volume is removed from the bag before addition of acetylcysteine.

This is different from current MHRA guidance which is to add the acetylcysteine volume to the bag leading to different infusion rates.

Notes/feedback

Feedback survey

https://forms.office.com/r/rExz13ftD6

Footnotes

If there is doubt about the timing of last paracetamol ingestion, it may be appropriate to use the time from the start of paracetamol overdose if this is known and to manage the patient as per the staggered paracetamol overdose pathway.

The risk of adverse drug reactions is greatest with the first bag of acetylcysteine due to the higher infusion rate compared to subsequent bags.

Disclaimer: this document has been designed to aid the medical management of typical patients who present with paracetamol overdose. It should be used in conjunction with TOXBASE guidance. Individual patients may need to be discussed with a senior clinician or with the NPIS.

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