BRITISH JOURNAL OF HOSPITAL MEDICINE

REVIEW

Toxicology in the emergency department: what's new?

Kenzo Motohashi[1]

Ruben HK Thanacoody[2]

Author details can be found at the end of this article

Correspondence to: Ruben HK Thanacoody; ruben.thanacoody@ncl.ac.uk

Abstract

Intentional and accidental drug overdose, recreational drug use and exposure to toxic substances are common reasons for people presenting to emergency departments. Although the mortality rate associated with these presentations is low in the UK, they can lead to significant morbidity and prolonged hospital admissions.

This review discusses new developments in the management of paracetamol overdose. Several new protocols for the infusion of acetylcysteine, the antidote for paracetamol overdose, have been proposed in the past decade and evaluated in clinical studies. The 12-hour Scottish and Newcastle Acetylcysteine Protocol regimen and 20-hour Australian two-infusion bag protocol have been widely adopted into clinical practice and endorsed in national guidelines because of their shorter duration, reduction in adverse effects and efficacy in treating overdose. This article includes a care pathway that can facilitate the implementation of the Scottish and Newcastle Acetylcysteine Protocol.

This article also discusses the emergency management of ingested button batteries, describes the emerging threat of novel psychoactive substances, and provides an update on new UK antidote guidelines. Further up-to-date guidance on management of clinical toxicology is available to healthcare professionals on the internet database TOXBASE.

Key words: Acetylcysteine; Antidotes; Antivenins; Care pathway; Drug overdose; Foreign bodies; Paracetamol; Psychotropic drugs

Submitted: 5 July 2022; accepted following double-blind peer review: 11 July 2022

Management of paracetamol overdose

Paracetamol is the drug that is most commonly taken in overdose in the UK, accounting for over 100 000 presentations to emergency departments and causing 100–150 deaths annually. It remains the most common cause of acute fulminant hepatic failure, necessitating liver transplantation.

Acetylcysteine

Acetylcysteine is highly effective at preventing liver toxicity in patients with paracetamol poisoning, especially when administered within 8 hours of paracetamol ingestion. The conventional intravenous acetylcysteine regimen is complex, involving three intravenous infusions each with different doses and infusion rates. The regimen is associated with a high frequency of dose-related adverse effects, especially vomiting and anaphylactoid reactions, which typically occur early during treatment when the acetylcysteine is being administered at a high infusion rate. A lower plasma paracetamol concentration is an additional risk factor for adverse effects resulting from administration of acetylcysteine.

The UK Medicines and Healthcare products Regulatory Agency's Commission on Human Medicines issued guidance on the management of paracetamol poisoning in 2012, recommending an increase in the duration of the first of the three acetylcysteine infusions from 150 mg/kg over 15 minutes to 150 mg/kg over 60 minutes (herein referred to as the 21-hour regimen). The change acted to bring UK guidance in line with the licensed regimen in the USA, despite evidence from a randomised controlled trial in Australia demonstrating no statistically significant difference in adverse effects between these two regimens (Kerr et al, 2005). Observational data from Edinburgh have also shown that there is no associated reduction in adverse effects with the slower 21-hour regimen compared with the faster regimen (Bateman et al, 2014a).

How to cite this article: Motohashi K, Thanacoody RHK. Toxicology in the emergency department: what's new? Br J Hosp Med. 2022. https://doi.org/10.12968/hmed.2022.0313

The fixed dose acetylcysteine regimen has further come under scrutiny after studies have described that some patients taking large paracetamol overdoses develop hepatotoxicity, despite early treatment within 8 hours (Cairney et al, 2016; Marks et al, 2017). This has sparked interest in modifying the existing 'one size fits all' acetylcysteine regimen to tailored regimens with fewer adverse effects.

New acetylcysteine regimens

Several acetylcysteine regimens have been proposed in the past decade. In the UK, a simpler and shorter infusion, known as the Scottish and Newcastle Acetylcysteine Protocol (SNAP), was developed using pharmacokinetic modelling to reduce the initial peak acetylcysteine concentrations and provide the same total dose of acetylcysteine (300 mg/kg) as the 21-hour regimen in two infusions: an initial loading infusion of 100 mg/kg over 2 hours followed by an infusion of 200 mg/kg over 10 hours (Figure 1) (Thanacoody et al, 2013a). A UK randomised controlled clinical trial demonstrated a significant reduction in the frequency of acetylcysteine-related adverse effects with the SNAP regimen compared with the 21-hour regimen (Bateman et al, 2014b).

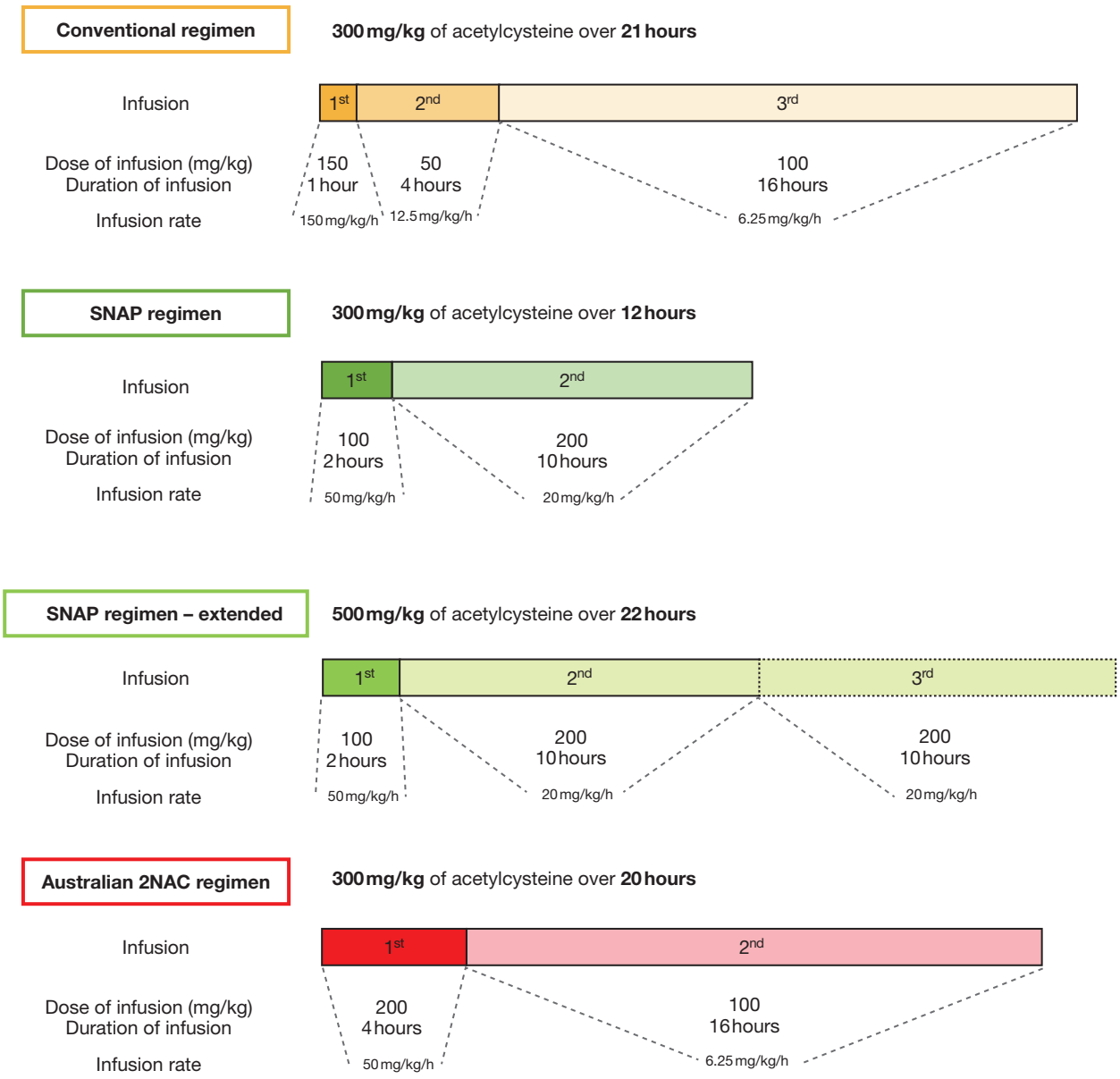


Figure 1. Acetylcysteine infusion regimens. 2NAC = 2-bag Australian Acetylcysteine Protocol; SNAP = Scottish and Newcastle Acetylcysteine Protocol.

The SNAP regimen was initially introduced into clinical practice at three hospitals in Edinburgh, Newcastle and London, with approval from their local medicines management committee. Clinical data were systematically collected as a prospective audit of patients treated with the SNAP regimen. Non-randomised comparisons of observed efficacy against available data from cohorts previously treated with other acetylcysteine regimens showed that the SNAP regimen was associated with a significantly reduced rate of anaphylactoid reactions. Crucially, the SNAP regimen was non-inferior to the 21-hour regimen in preventing acute liver injury in all patterns of paracetamol overdose, namely acute single overdoses, staggered overdoses and chronic therapeutic excess (Pettie et al, 2019).

In Australia, an alternative two-infusion regimen was developed, consisting of a slower initial infusion of 200 mg/kg for 4 hours (50 mg/kg/h) followed by 100 mg/kg over 16 hours. A non-randomised observational study showed that, when compared with the 21-hour regimen, this two-infusion regimen was associated with a reduced rate of adverse effects and was similarly effective in preventing liver injury (Wong et al, 2020). The two-infusion regimen is recommended as the preferred acetylcysteine regimen in Australia and New Zealand guidelines (Chiew et al, 2020).

High dose acetylcysteine for patients at high risk of hepatotoxicity

Both the SNAP and Australian two-infusion regimen use a slower loading infusion rate of 50 mg/kg/h but the SNAP regimen delivers the total dose in 12 hours rather than 20 hours. At the end of the 12-hour SNAP regimen, the 200 mg/kg infusion over 10 hours can be repeated, providing a total acetylcysteine dose of 500 mg/kg over 22 hours (*Figure 1*). Studies have investigated the use of higher dose acetylcysteine for treating patients with large overdoses.

The ATOM-2 study was an observational study of 79 patients with massive paracetamol overdose presenting to several Australian hospitals (Chiew et al, 2017). These patients had a 4-hour extrapolated paracetamol concentration of more than 300 mg/litre (ie above the 300 mg/litre nomogram line) and were treated within 16 hours of overdose with either the conventional 21-hour acetylcysteine regimen or an increased acetylcysteine dose consisting of at least doubling the dose of the 16-hourly infusion to 200 mg/kg, giving a total dose of 400 mg/kg or more over 21 hours. The higher acetylcysteine dose was associated with a significant reduction in the rates of hepatotoxicity, with a rate of 10 out of 36 (27.7%) in the standard regimen group and 4 out of 43 (9.3%) in the higher acetylcysteine dose group.

In a retrospective cohort study of 373 patients presenting with an extrapolated paracetamol concentration of more than 300 mg/litre in the USA, 135 patients received standard intravenous acetylcysteine, 121 patients received oral acetylcysteine (140 mg/kg loading dose followed by 70 mg/kg every 4 hours for four doses, giving a total of 420 mg/kg) and 117 patients received high-dose intravenous acetylcysteine (150 mg/kg intravenous loading dose followed by 50 mg/kg infusion over 4 hours followed by 200 mg/kg infusion over 16 hours, giving a total of 400 mg/kg). There was no statistical difference in the risk of developing hepatotoxicity between the standard dose intravenous acetylcysteine and either the high dose intravenous acetylcysteine (15.4% vs 14.8%) or oral acetylcysteine (10.7% vs 14.8%) (Lewis et al, 2022). There was one fatality in the high dose intravenous acetylcysteine group.

A similar proportion of patients with paracetamol concentrations above the 300 mg/litre nomogram line who were treated with the SNAP protocol within 16 hours (9.8%) and 24 hours (15%) developed hepatotoxicity when compared to the studies described above (Alrossies et al, 2022).

A single-bag regimen consisting of an infusion of 150 mg/kg over 1 hour followed by 15 mg/kg/hour has also been described (Shah and Beuhler, 2022). In a small retrospective poison centre study in the USA, comparing this high-dose single infusion to the conventional three-bag 21-hour regimen in patients at high risk of hepatotoxicity (defined as an alanine transaminase*paracetamol multiplication product >10 000 at presentation), 19 out of 66 (29%) treated with the single infusion developed hepatotoxicity (peak alanine transaminase >1000U/litre) compared to 12 out of 23 (52%) treated with the 21-hour regimen. However, acute overdoses represented only around half of the patients and those treated within 8 hours were excluded from the study.

Scottish and Newcastle Acetylcysteine Protocol

Given the advantages of the SNAP regimen in terms of reduction of adverse effects, a shorter infusion time potentially reducing length of hospital stay, as well as the ability to tailor the regimen to provide a higher dose at the end of the 12-hour infusion in selected patients, the Royal College of Emergency Medicine (2021a) recommended that the SNAP regimen be used as standard care in emergency departments in the UK. Although the SNAP regimen delivers the same licensed dose as the 21-hour regimen, it is an off-label use of a new regimen and requires local clinical governance approvals before implementation. The authors have developed a simple flowchart (**Figure 2**) and clinical care pathways to facilitate the implementation of the SNAP protocol in routine clinical practice in adults and children more than 6 years old (**Appendix 1**) and children under 6 years old (**Appendix 2**).

Novel biomarkers and antidotes

For over 40 years, the paracetamol treatment nomogram has been used to risk-assess patients and acetylcysteine has been the mainstay of treatment for treatment of paracetamol overdose. Novel biomarkers are being investigated to identify patients at risk of developing hepatotoxicity and enable stratified trials of newer antidotes in high-risk patients. Novel biomarkers such as miR-122, HMGB1 and keratin-18 appear to be better predictors of hepatotoxicity than paracetamol concentration (Dear et al, 2018).

Calmangafodipir, a superoxide dismutase mimetic, has been identified as an agent which may prevent paracetamol-induced liver toxicity by reducing the free radical damage that is caused by paracetamol overdose. It was well tolerated in a phase 1 clinical trial (Morrison et al, 2019) and is currently undergoing evaluation of efficacy in a phase 2/3 trial.

Fomepizole, an antidote used to treat toxic alcohol poisoning through inhibition of alcohol dehydrogenase, is also an inhibitor of CYP2E1, the main cytochrome isoform involved in the metabolism of paracetamol to its hepatotoxic intermediate metabolite *N*-acetyl-para-benzoquinone imine (NAPQI). Fomepizole has been used as an adjunct to acetylcysteine in a case series of patients taking massive paracetamol overdose (Shah et al, 2021), but requires formal evaluation in a randomised clinical trial to determine whether it has a place in the management of paracetamol overdose (Akakpo et al, 2022).

Management of button battery ingestions

Injury from button batteries

Button batteries are a common component of many household devices and can cause severe injury if ingested. Although uncommon, the majority of cases involve children under the age of 5 years. The incidence of severe injury and the number of fatalities appears to have increased since the introduction of larger (>20 mm) lithium batteries. These larger batteries are more likely to become lodged in the oesophagus and therefore have a longer duration of contact with oesophageal tissue, leading to hydrolysis of water into hydroxide ions, which cause caustic injury with liquefactive necrosis. Potentially life-threatening features reported after ingestion include oesophageal burns and haemorrhage, and in more severe cases, perforation and stricture formation (Litovitz et al, 2010). Fatalities as a result of haemorrhage or aorto-oesophageal fistulas have been reported even after the battery has been removed endoscopically.

Neutralising agents

New recommendations for the management of button battery ingestion have been published as a position statement by the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (Mubarak et al, 2021). These reflect the findings of in vitro and in vivo animal studies describing a lower incidence of full-thickness injury associated with the use of honey or sucralfate as neutralising agents (Anfang et al, 2019). These recommendations include early administration of honey in the prehospital setting and/or administration of sucralfate in hospital before endoscopic removal of batteries lodged in the oesophagus. Both of these agents are weak acids that can form a physical barrier around the battery and may neutralise the alkaline environment developing in the oesophageal mucosa as a result of contact with the battery.

A separate in vitro study described the neutralising effect of sterile acetic acid on oesophageal tissue when it was used as an irrigation fluid after the button battery was removed at endoscopy. Reduction of tissue pH was noted even after prolonged exposure

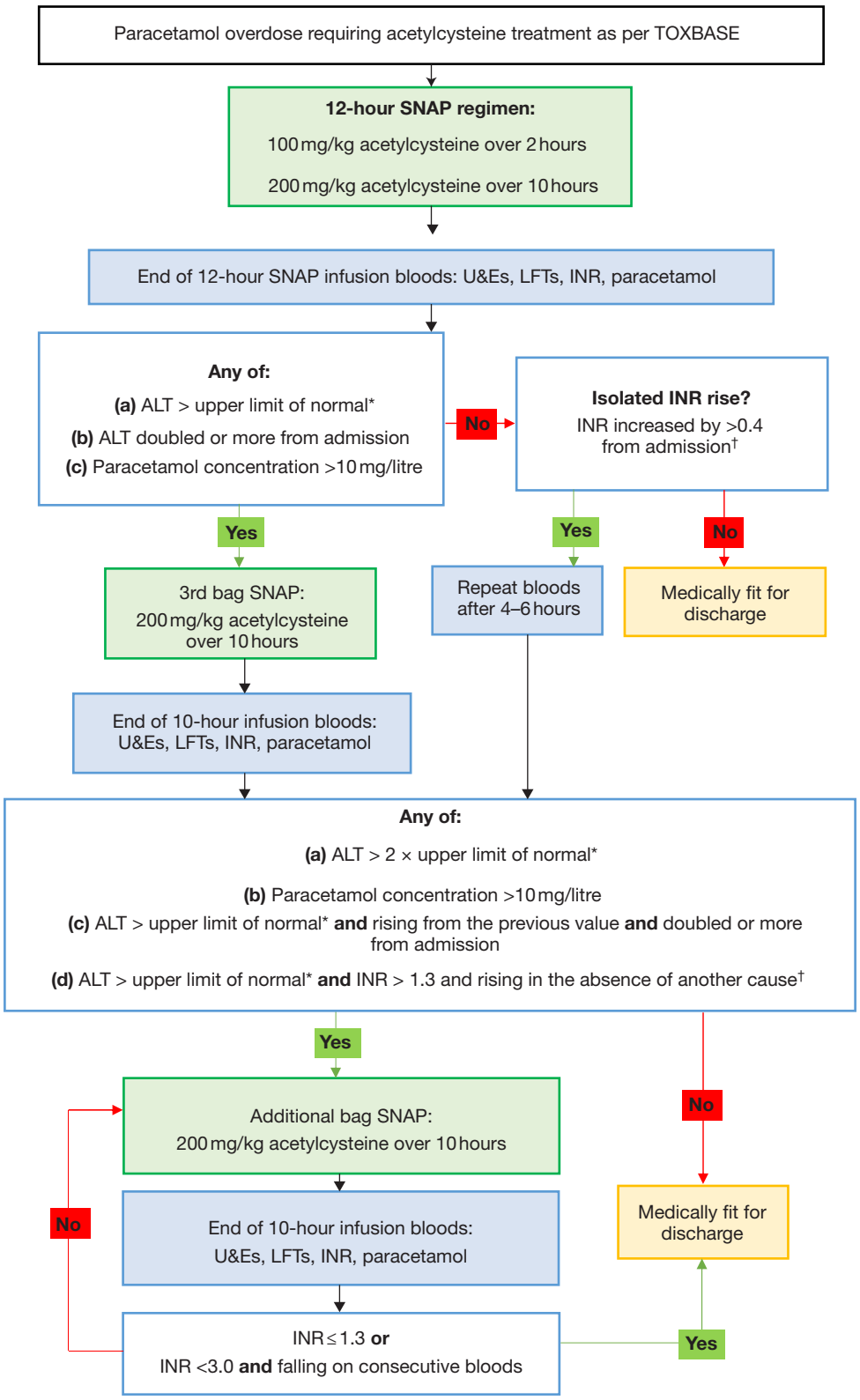


Figure 2. Scottish and Newcastle Acetylcysteine Protocol (SNAP) flowchart. *In patients with chronically elevated ALT levels, acetylcysteine may be discontinued if the ALT level is abnormal but unchanged or fallen from the previous value. †in the absence of another cause, eg warfarin. ALT = alanine transaminase; INR = international normalised ratio; LFT = liver function tests; U&E = urea and electrolytes.

to the button battery (Jatana et al, 2017). Improvement in the clinical appearance of the oesophagus after irrigation with sterile 0.25% acetic acid was seen in six paediatric patients following endoscopic removal of a button battery (Jatana et al, 2019).

Novel psychoactive substances

Drug misuse remains prevalent, with 1 in 3 adults in the UK reporting having used a recreational drug at some point in their lives (Home Office, 2019), and acute toxicity following recreational drug use is a common presentation to emergency departments. The pattern of illicit drug use has evolved over the last decade with the global emergence of over 1000 novel psychoactive substances identified to date. Novel psychoactive substances are often chemically and clinically similar to traditional drugs of misuse but with alterations to the chemical structure to avoid legal prohibition. Novel psychoactive substances pose a public health threat comparable to traditional drugs. Hospital admissions and drug-related deaths have been rising in the UK, with opioids accounting for around half of the deaths but mortality from cocaine and novel psychoactive substances is also rising. Although sometimes misleadingly sold as 'legal highs', all psychoactive substances (with some exceptions) not already regulated under the Misuse of Drugs Act became controlled under the Psychoactive Substances Act in the UK in 2016 (Shafi et al, 2020).

Bedside immunoassay tests and urine toxicology screens can only detect a small number of classical drugs and not novel psychoactive substances, so a negative test does not exclude exposure to novel psychoactive substances. Analytical confirmation by mass spectrometry is the gold standard, but is not routinely available to influence the clinical management of the patients. Mass spectrometry remains useful for surveillance purposes, for example, the ongoing IONA study (Identification of Novel Psychoactive Substances: https://research.ncl.ac.uk/iona/) aims to undertake analytical confirmation in blood and urine samples from patients presenting to emergency departments in the UK following exposure to any recreational drug.

Therefore, clinical management relies on toxidrome assessment and familiarity with the changing patterns of drug use regionally. Examples of classical drugs and novel psychoactive substances associated with different toxidromes are shown in Table 1.

Antidote availability

Antidotes are available for the treatment of some overdoses and can be life-saving. National audits have previously highlighted inadequate stocking of some rarely used antidotes (Thanacoody et al, 2013b) and led to the UK National Poisons Information Service and Royal College of Emergency Medicine issuing joint guidelines on the availability of antidotes in emergency departments (Royal College of Emergency Medicine, 2021b). Antidotes added to the guidelines in the latest update include andexanet alfa for the reversal of gastrointestinal bleeding from apixaban and rivaroxaban, L-carnitine for the treatment of severe valproate toxicity and ViperFav for the treatment of European adder envenomation.

In England, eight antidote holding centres have been set up to stock category C (supra-regionally held) antidotes for the treatment of poisoning with thallium (Prussian Blue), lead (sodium calcium edetate and succimer) and mercury (Unithiol). Two antidotes, glucarpidase and uridine triacetate, are commissioned by NHS England and available on a named-patient basis directly from the supplier within 24 hours for the management of methotrexate-induced renal dysfunction and capecitabine or 5-fluorouracil toxicity respectively.

There are centralised arrangements in the UK for the provision of specific antivenoms for the treatment of envenomation from non-indigenous snakes. The need for treatment with these antidotes should be discussed with a consultant clinical toxicologist or the National Poisons Information Service.

Conclusions

Research in toxicology has led to important advances in recent years, including identifying new psychoactive substances, optimising acetylcysteine for paracetamol overdose, improved availability of rarely used antidotes and clinical trials of new antidotes. In the UK, up-to-date

Table 1. Classification of classical and novel psychoactive substances

Toxidrome	Classical drugs	Novel psychoactive substances
Stimulant	Amphetamines, cocaine	Substituted amphetamines, eg 4-methylamphetamine
		Synthetic cocaines, eg dimethocaine
		Aminoindanes, eg 5,6-methylenedioxy-2-aminoindane
		Benzofurans, eg 6-(2-aminopropyl)benzofuran
		Cathinones, eg 4-methylmethcathinone (mephedrone)
		Piperazines, eg benzylpiperazine
		Pipradol derivatives, eg desoxypipradol, diphenylprolinol
		Thiophenes, eg methiopropramine
Depressant	Opioids, eg heroin, methadone	Fentanyls, eg carfentanil, acetylfentanil, furanylfentanil
	Benzodiazepines, eg diazepam	Benzimidazole opioids, eg isotonitazene, etonitazene
		Novel benzodiazepines, eg flualprazolam, etizolam
Cannabinoid	Cannabis	Synthetic cannabinoid receptor agonists, eg JWH-018, MDMB-CHMICA, 5F-MDMB-PINACA
Hallucinogenic	Lysergic acid diethylamide (LSD), psilocin	Tryptamines, eg alpha-methyltryptamine
		Benzodifurans, eg BromodragonFLY
		Lysergamines, eg 1-acetyl-LSD
		Phenethylamines, eg 25I-NBOMe
Dissociative	Ketamine, phencyclidine	Methoxetamine
		Diphenidine

advice on management of poisoning is available via the UK National Poisons Information Service through a national telephone service and TOXBASE, a web-based information database that is available free of charge to healthcare professionals.

Author details

[1]Translational and Clinical Research Institute, Newcastle University, Newcastle-upon-Tyne, UK

[2]National Poisons Information Service (Newcastle Unit), Newcastle-upon-Tyne Hospitals NHS Foundation Trust, Newcastle-upon-Tyne, UK

Conflicts of interest

The authors declare that there are no conflicts of interest.

Key points

- A new shorter acetylcysteine regimen, the Scottish and Newcastle Acetylcysteine Protocol, may be used to treat patients with paracetamol overdose. Its use reduces adverse effects and length of hospital stay.
- Prehospital administration of honey and/or sucralfate administration in hospital and irrigation with sterile acetic acid following endoscopic removal of button batteries impacted in the oesophagus can mitigate oesophageal injury.
- Novel psychoactive substances are increasingly used for recreational purposes and active surveillance is necessary to identify new emerging public health threats.
- Centralised arrangements are available in the UK to improve availability of some rarely used but potentially life-saving antidotes and antivenoms. These can be accessed after discussion with the UK National Poisons Information Service (0344 892 0111).

References

Akakpo JY, Ramachandran A, Curry SC et al. Comparing N-acetylcysteine and 4-methylpyrazole as antidotes for acetaminophen overdose. Arch Toxicol. 2022;96(2):453–465. https://doi.org/10.1007/s00204-021-03211-z

Alrossies AS, Motohashi K, Wiltshire S et al. Efficacy of 12h intravenous acetylcysteine (SNAP) regimen following large single acute paracetamol overdose. Clin Toxicol. 2022;60:84–85

Anfang RR, Jatana KR, Linn RL et al. pH-neutralizing esophageal irrigations as a novel mitigation strategy for button battery injury. Laryngoscope. 2019;129(1):49–57. https://doi.org/10.1002/lary.27312

Bateman DN, Carroll R, Pettie J et al. Effect of the UK's revised paracetamol poisoning management guidelines on admissions, adverse reactions and costs of treatment. Br J Clin Pharmacol. 2014a;78(3):610–618. https://doi.org/10.1111/bcp.12362

Bateman DN, Dear JW, Thanacoody HK et al. Reduction of adverse effects from intravenous acetylcysteine treatment for paracetamol poisoning: a randomised controlled trial. Lancet. 2014b;383(9918):697–704. https://doi.org/10.1016/S0140-6736(13)62062-0

Cairney DG, Beckwith HKS, Al-Hourani K et al. Plasma paracetamol concentration at hospital presentation has a dose-dependent relationship with liver injury despite prompt treatment with intravenous acetylcysteine. Clin Toxicol (Phila). 2016;54(5):405–410. https://doi.org/10.3109/15563650.2016.1159309

Chiew AL, Isbister GK, Kirby KA et al. Massive paracetamol overdose: an observational study of the effect of activated charcoal and increased acetylcysteine dose (ATOM-2). Clin Toxicol. 2017;55(10):1055–1065. https://doi.org/10.1080/15563650.2017.1334915

Chiew AL, Reith D, Pomerleau A et al. Updated guidelines for the management of paracetamol poisoning in Australia and New Zealand. Med J Aust. 2020;212(4):175–183. https://doi.org/10.5694/mja2.50428

Dear JW, Clarke JI, Francis B et al. Risk stratification after paracetamol overdose using mechanistic biomarkers: results from two prospective cohort studies. Lancet Gastroenterol Hepatol. 2018;3(2):104–113. https://doi.org/10.1016/S2468-1253(17)30266-2

Home Office. Drug misuse: findings from the 2018 to 2019 CSEW. 2019. https://www.gov.uk/government/statistics/drug-misuse-findings-from-the-2018-to-2019-csew (accessed 11 August 2022)

Jatana KR, Rhoades K, Milkovich S et al. Basic mechanism of button battery ingestion injuries and novel mitigation strategies after diagnosis and removal. Laryngoscope. 2017;127(6):1276–1282. https://doi.org/10.1002/lary.26362

Jatana KR, Barron CL, Jacobs IN. Initial clinical application of tissue pH neutralization after esophageal button battery removal in children. Laryngoscope. 2019;129(8):1772–1776. https://doi.org/10.1002/lary.27904

Kerr F, Dawson A, Whyte IM et al. The Australasian Clinical Toxicology Investigators Collaboration randomized trial of different loading infusion rates of N-acetylcysteine. Ann Emerg Med. 2005;45(4):402–408. https://doi.org/10.1016/j.annemergmed.2004.08.040

Lewis JC, Lim M, Lai L et al. Evaluation of N-acetylcysteine dose for the treatment of massive acetaminophen ingestion. Clin Toxicol. 2022;60(4):507–513. https://doi.org/10.1080/15563650.2021.1984503

Litovitz T, Whitaker N, Clark L et al. Emerging battery-ingestion hazard: clinical implications. Pediatrics. 2010;125(6):1168–1177. https://doi.org/10.1542/peds.2009-3037

Marks DJ, Dargan PI, Archer JR et al. Outcomes from massive paracetamol overdose: a retrospective observational study. Br J Clin Pharmacol. 2017;83(6):1263–1272. https://doi.org/10.1111/bcp.13214

Morrison EE, Oatey K, Gallagher B et al. Principal results of a randomised open label exploratory, safety and tolerability study with calmangafodipir in patients treated with a 12 h regimen of N-acetylcysteine for paracetamol overdose (POP trial). EBioMedicine. 2019;46:423–430. https://doi.org/10.1016/j.ebiom.2019.07.013

Mubarak A, Benning MA, Broekaert I et al. Diagnosis, management and prevention of button battery ingestion in childhood: an ESPGHAN position paper. J Pediatr Gastroenterol Nutr. 2021;73(1):129–136. https://doi.org/10.1097/MPG.0000000000003048

Pettie JM, Caparrotta TM, Hunter RW et al. Safety and efficacy of the SNAP 12h acetylcysteine regimen for the treatment of paracetamol overdose. EClinicalMedicine. 2019;11:11–17. https://doi.org/10.1016/j.eclinm.2019.04.005

Royal College of Emergency Medicine. RCEM position statement. Use of the SNAP regime for the treatment of paracetamol toxicity. 2021a. https://rcem.ac.uk/wp-content/uploads/2021/11/Use_of_SNAP_for_Treatment_of_Paracetamol_Toxicity_Nov_2021.pdf (accessed 15 July 2022)

Royal College of Emergency Medicine. Royal College of Emergency Medicine and National Poisons Information Service Guideline on Antidote. 2021b. https://rcem.ac.uk/rcem-npis-antidote-guideline-update-2021/ (accessed 15 July 2022)

Shafi A, Berry AJ, Sumnall H et al. New psychoactive substances: a review and updates. Ther Adv Psychopharmacol. 2020;10:204512532096719. https://doi.org/10.1177/2045125320967197

Shah KR, Beuhler MC. Single bag high dose intravenous N-acetylcysteine associated with decreased hepatotoxicity compared to triple bag intravenous N-acetylcysteine in high-risk acetaminophen ingestions. Clin Toxicol (Phila). 2022;60(4):493–498. https://doi.org/10.1080/15563650.2021.197923

Shah KR, Fox C, Geib AJ et al. Fomepizole as an adjunctive treatment in severe acetaminophen ingestions: a case series. Clin Toxicol. 2021;59(1):71–72. https://doi.org/10.1080/15563650.2020.1775847

Thanacoody HK, Gray A, Dear JW et al. Scottish and Newcastle antiemetic pre-treatment for paracetamol poisoning study (SNAP). BMC Pharmacol Toxicol. 2013a;14(1):20. https://doi.org/10.1186/2050-6511-14-20

Thanacoody RH, Aldridge G, Laing W et al. National audit of antidote stocking in acute hospitals in the UK. Emerg Med J. 2013b;30(5):393–396. https://doi.org/10.1136/emermed-2012-201224

Wong A, Isbister G, McNulty R et al. Efficacy of a two-bag acetylcysteine regimen to treat paracetamol overdose (2NAC study). EClinicalMedicine. 2020;20:100288. https://doi.org/10.1016/j.eclinm.2020.100288

Appendix 1. SNAP care pathway Adults and children over 6 years old.

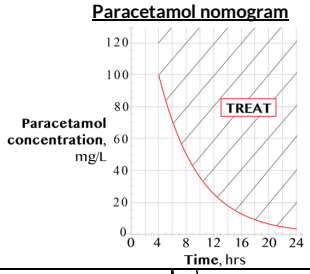
Management of Paracetamol Overdose
in adults and children over 6 years old
SNAP 12-hour regimen

MRN:
Name:
DOB:
Address:
addressograph

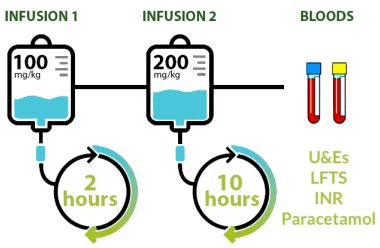
1	Initial Evaluation	
	Date of **presentation**: ___/___/___ **Time** at presentation: ___:___ **Date** of **last ingestion**: ___/___/___ **Time** at last ingestion: ___:___ **Time since** last ingestion: _____ hours *tick one:* ☐ <8h ☐ 8-24h ☐ >24h ☐ Unknown	Total **overdose**: _____ **g** Patient **weight**: _____ **kg** Overdose **per weight**: _____ **mg/kg** (use pre-pregnancy weight if pregnant & max. weight as 110kg) **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** >licensed daily dose for ≥2 days)

2	Management		Sign	Date/Time
A	**A**ctivated charcoal	Adult dose: 50g; Children dose: 1g/kg		
	Consider if ***all*** :	☐ **Airway** is protected ☐ Presents within **1 hour** ☐ Overdose **>150 mg/kg**		
B	**B**lood 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 over **8h** 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 (≤ upper limit of normal, ULN) ☐ **INR** is normal (≤ 1.3) ☐ Patient is **asymptomatic**		

Paracetamol nomogram



SNAP 12-hour acetylcysteine regimen



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** > ULN (consider specialist advice if chronically elevated) ☐ **INR** > 1.3 (consider specialist advice if chronically elevated)		

V.3, June-21. Newcastle upon Tyne Hospitals NHS Foundation Trust. Page 1 of 3

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 >ULN	**OR**	ALT doubled or more from admission (≥2× admission ALT)	**OR**	Paracetamol concentration > 10mg/L		
Repeat bloods after 4-6 hours if **isolated INR rise:**		INR increased by >0.4 from admission	**&**	Normal ALT (≤ULN) **AND** ALT less than doubled since admission	**&**	Paracetamol concentration ≤ 10mg/L		
Medically fit for discharge if ***all*** **:**		INR increased by ≤0.4 from admission	**&**	Normal ALT (≤ULN) **AND** ALT less than doubled since admission	**&**	Paracetamol concentration ≤ 10mg/L		

° 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 or the repeat bloods for an isolated INR rise are abnormal, i.e., **any of**:
  a) ALT > 2 × upper limit of normal (ULN),
  b) ALT > ULN **AND** rising from the previous value **AND** doubled or more from admission,
  c) ALT > ULN **AND** INR > 1.3 and rising in the absence of another cause,
  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)**	4-hour repeat	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

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.

Appendix 2. SNAP care pathway children under 6 years old.

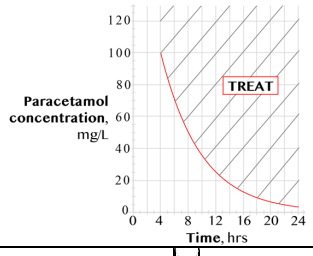
Management of Paracetamol Overdose
in children under 6 years old
SNAP 12-hour regimen

MRN:
Name: addressograph
DOB:
Address:

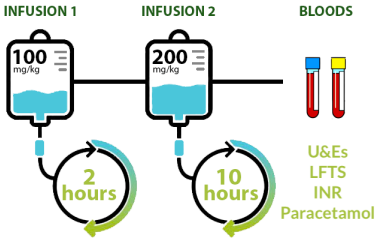
1	Initial Evaluation	
	Date of **presentation**: ___/___/___ **Time** at presentation: ___:___ **Date** of **last ingestion**: ___/___/___ **Time** at last ingestion: ___:___ **Time since** last ingestion: _____ hours *tick one:* ☐ <8h ☐ 8-24h ☐ >24h ☐ Unknown	Total **overdose**: _____ **g** Patient **weight**: _____ **kg** Overdose **per weight**: _____ **mg/kg** **Pattern** of ingestion (*tick one if known*) : ☐ Single acute overdose (≥150mg/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** >licensed daily dose for ≥2 days)

2	Management		Sign	Date/Time
A	**A**ctivated charcoal	Dose: 1g/kg (max. 50g)		
	Consider if ***all*** :	**Airway** is protected		
		Presents within **1 hour**		
		Overdose **>150 mg/kg**		
B	**B**lood tests	FBC, U&Es, LFT, 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 over **8h** 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 (≤ upper limit of normal, ULN)		
		INR is normal (≤ 1.3)		
		Patient is **asymptomatic**		

Paracetamol nomogram



SNAP 12-hour acetylcysteine regimen



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 > ULN (consider specialist advice if chronically elevated)		
		INR > 1.3 (consider specialist advice if chronically elevated)		

V.3, June-21. Newcastle upon Tyne Hospitals NHS Foundation Trust. Page 1 of 4

D	**Drug reactions**	Recognise: nausea, vomiting, flushing, urticarial rash, angioedema, tachycardia, wheeze.						
Consider taking the following actions:		☐ *Temporarily* **stop** the acetylcysteine infusion						
		☐ IV **chlorphenamine** 2.5 mg (6 months to 5 years old)						
		☐ 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 >ULN	**OR**	ALT doubled or more from admission (≥2× admission ALT)	**OR**	Paracetamol concentration > 10mg/L		
Repeat bloods after 4-6 hours if **isolated INR rise:**		INR increased by >0.4 from admission	**&**	Normal ALT (≤ULN) **AND** ALT less than doubled since admission	**&**	Paracetamol concentration ≤ 10mg/L		
Medically fit for discharge if ***all*** **:**		INR increased by ≤0.4 from admission	**&**	Normal ALT (≤ULN) **AND** ALT less than doubled since admission	**&**	Paracetamol concentration ≤ 10mg/L		

° 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 or the repeat bloods for an isolated INR rise are abnormal, i.e., **any of**:
  a) ALT > 2 × upper limit of normal (ULN),
  b) ALT > ULN **AND** rising from the previous value **AND** doubled or more from admission,
  c) ALT > ULN **AND** INR > 1.3 and rising in the absence of another cause,
  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)**	**4-hour repeat**	**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

Acetylcysteine Dosing Table Children under 40kg							
	First Infusion			Second (and additional) Infusions			
Infusion **fluid**	5% glucose or 0.9% sodium chloride			5% glucose or 0.9% sodium chloride			Infusion **fluid**
Infusion **duration**	2 hours			10 hours			Infusion **duration**
Acetylcysteine dose	**100 mg/kg**			**200 mg/kg**			**Acetylcysteine dose**
Infusion **concentration**	50 mg/mL			10 mg/mL			Infusion **concentration**
Preparation	Dilute each 10mL acetylcysteine with 30mL of diluent			Dilute each 10mL acetylecysteine with 190mL of diluent			Preparation
Patient **Weight** (kg)	Acetylcysteine **volume** (mL)	Infusion **Rate** (mL/h)	Stock solution	Acetylcysteine **volume** (mL)	Infusion **Rate** (mL/h)	Stock solution	Patient **Weight** (kg)
5	10	5	1 x 10mL acetylcysteine, 30mL diluent	100	10	1 x 10mL acetylcysteine, 190mL diluent	5
6	12	6		120	12		6
7	14	7		140	14		7
8	16	8		160	16		8
9	18	9		180	18		9
10-14	24	12		240	24	2 x 10mL acetylcysteine, 380mL diluent	10-14
15-19	34	17		340	34		15-19
20-24	44	22	2 x 10mL acetylcysteine, 60mL diluent	440	44	3 x 10mL acetylcysteine, 570mL diluent	20-24
25-29	54	27		540	54		25-29
30 - 34	64	32		640	64	4 x 10mL acetylcysteine, 760mL diluent	30 - 34
35 - 39	74	37		740	74		35 - 39

10mL ampoules of **200 mg/mL** acetylcysteine

SNAP	Acetylcysteine Dosing Table Children over 40kg			
	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/UyGrXMfhTF

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.