

Toxicology in the emergency department: what's new?

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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

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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).

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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 (300mg/kg) as the 21-hour regimen in two infusions: an initial loading infusion of 100mg/kg over 2 hours followed by an infusion of 200mg/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).

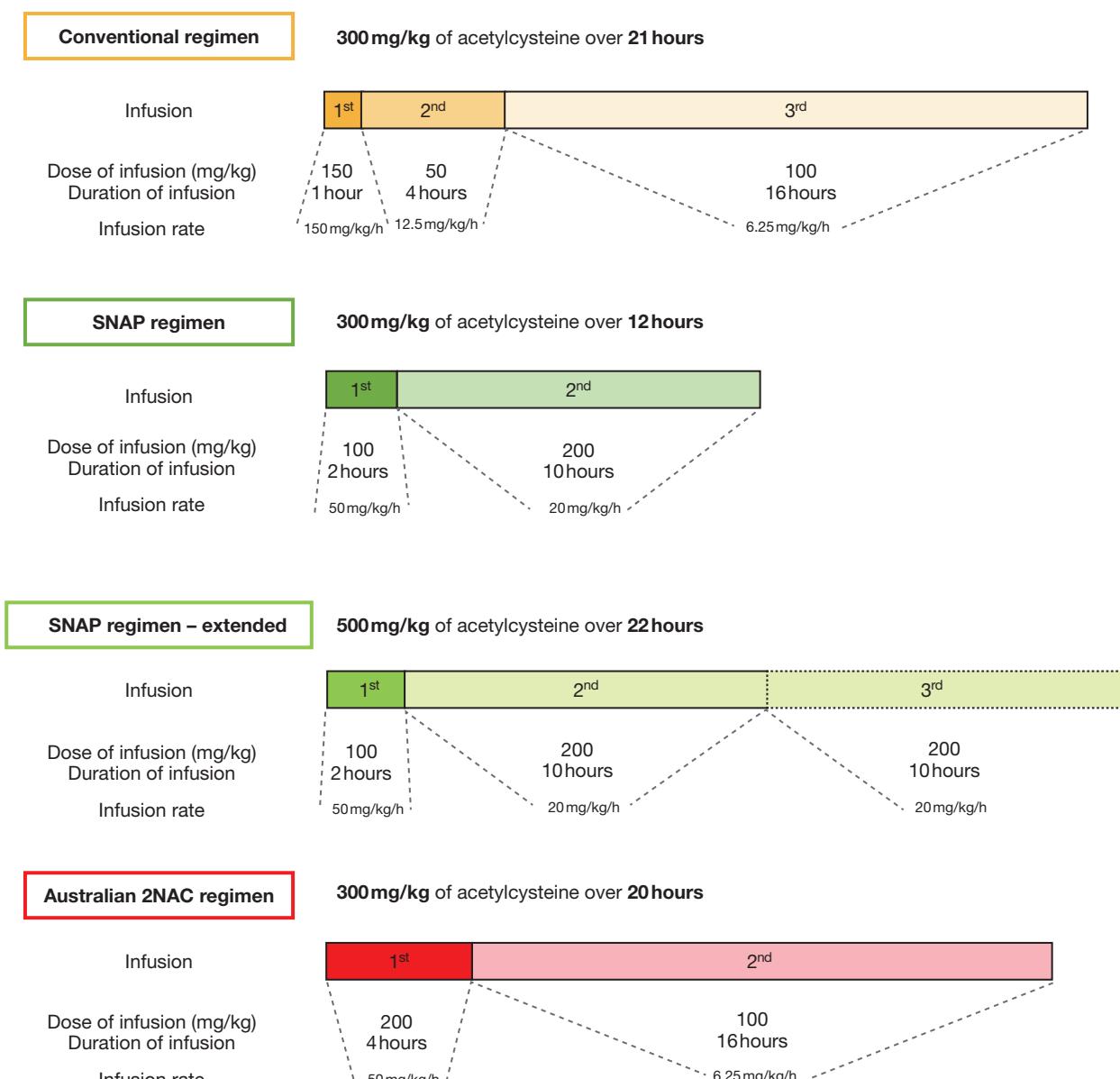


Figure 1. Acetylcysteine infusion regimens. 2NAC = 2-bag Australian Acetylcysteine Protocol; SNAP = Scottish and Newcastle Acetylcysteine Protocol.

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 >1000 U/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 (>20mm) 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

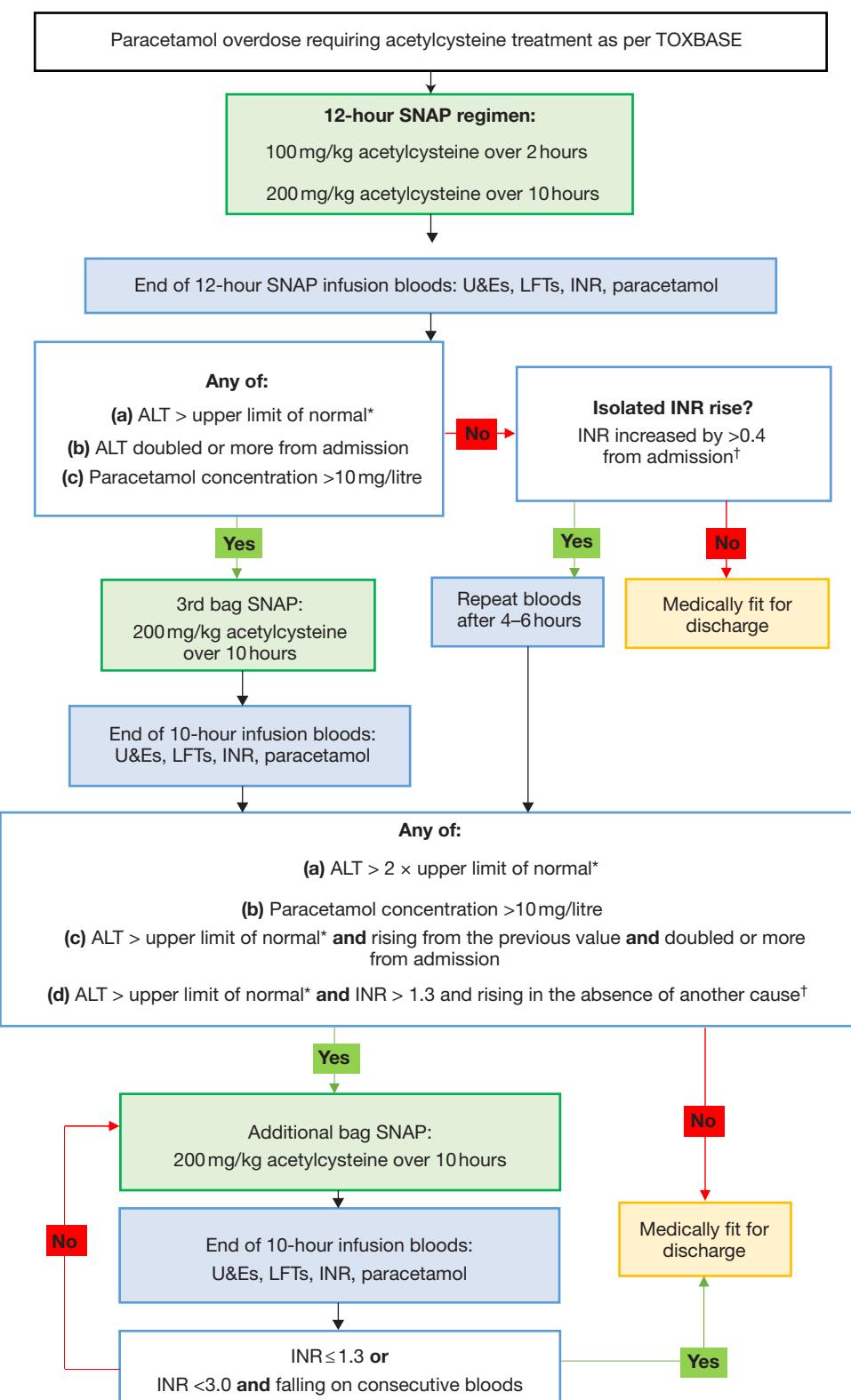


Figure 2. Scottish and Newcastle Acetylcysteine Protocol (SNAP) flowchart. *In patients with chronically elevated ALT levels, acetylcysteine may be discontinued if the ALT level is abnormal but unchanged or fallen from the previous value. †in the absence of another cause, eg warfarin. ALT = alanine transaminase; 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 Benzodiazepines, eg diazepam	Fentanyl, eg carfentanil, acetyl fentanyl, furanyl fentanyl 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.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

Key points

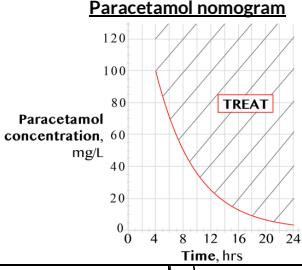
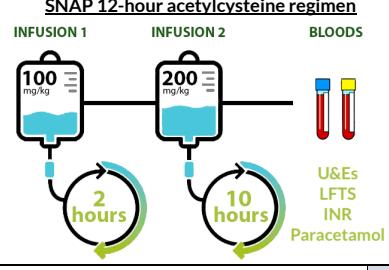
- A new shorter acetylcysteine regimen, the Scottish and Newcastle Acetylcysteine Protocol, may be used to treat patients with paracetamol overdose. Its use reduces adverse effects and length of hospital stay.
- Prehospital administration of honey and/or sucralfate administration in hospital and irrigation 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).

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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: _____									
1 Initial Evaluation											
Date of presentation: _____ / _____ / _____ Time at presentation: _____ : _____ Date of last ingestion: _____ / _____ / _____ Time at last ingestion: _____ : _____ Time since last ingestion: _____ hours tick one: <input type="checkbox"/> <8h <input type="checkbox"/> 8-24h <input type="checkbox"/> >24h <input type="checkbox"/> Unknown		Total overdose: _____ g (use pre-pregnancy weight if pregnant & max. weight as 110kg) Patient weight: _____ kg Overdose per weight: _____ mg/kg Pattern of ingestion (tick one if known): <input type="checkbox"/> Single acute overdose ($\geq 75\text{mg/kg}$ over a period 1 hour or less) <input type="checkbox"/> Staggered overdose ($\geq 75\text{mg/kg}$ over more than 1 hour AND deliberate self-harm) <input type="checkbox"/> Therapeutic excess ($\geq 75\text{mg/kg}$ over 24 hours OR >licensed daily dose for ≥ 2 days)									
2 Management											
A	Activated charcoal Adult dose: 50g; Children dose: 1g/kg Consider if all : <table border="0" style="width: 100%;"> <tr> <td style="width: 20%;"><input type="checkbox"/> Airway is protected</td> <td style="width: 20%;"><input type="checkbox"/> Presents within 1 hour</td> <td style="width: 20%;"><input type="checkbox"/> Overdose $> 150\text{ mg/kg}$</td> <td style="width: 20%;"></td> </tr> </table>	<input type="checkbox"/> Airway is protected	<input type="checkbox"/> Presents within 1 hour	<input type="checkbox"/> Overdose $> 150\text{ mg/kg}$		Sign	Date/Time				
<input type="checkbox"/> Airway is protected	<input type="checkbox"/> Presents within 1 hour	<input type="checkbox"/> Overdose $> 150\text{ mg/kg}$									
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: <table border="0" style="width: 100%;"> <tr> <td style="width: 20%;"><input type="checkbox"/> Single acute overdose $> 150\text{mg/kg}$ & last ingestion over 8h ago</td> <td style="width: 20%;"><input type="checkbox"/> Single acute overdose $> 150\text{mg/kg}$ & unknown time of ingestion</td> <td style="width: 20%;"><input type="checkbox"/> Staggered overdose</td> <td style="width: 20%;"><input type="checkbox"/> Clinical features of liver toxicity (e.g., jaundice, liver tenderness)</td> </tr> </table> ii Stop acetylcysteine after admission blood results if all: <table border="0" style="width: 100%;"> <tr> <td style="width: 20%;"><input type="checkbox"/> Paracetamol concentration $< 10\text{mg/L}$ or below the treatment line on the nomogram</td> <td style="width: 20%;"><input type="checkbox"/> ALT is normal (\leq upper limit of normal, ULN)</td> <td style="width: 20%;"><input type="checkbox"/> INR is normal (≤ 1.3)</td> <td style="width: 20%;"><input type="checkbox"/> Patient is asymptomatic</td> </tr> </table>	<input type="checkbox"/> Single acute overdose $> 150\text{mg/kg}$ & last ingestion over 8h ago	<input type="checkbox"/> Single acute overdose $> 150\text{mg/kg}$ & unknown time of ingestion	<input type="checkbox"/> Staggered overdose	<input type="checkbox"/> Clinical features of liver toxicity (e.g., jaundice, liver tenderness)	<input type="checkbox"/> Paracetamol concentration $< 10\text{mg/L}$ or below the treatment line on the nomogram	<input type="checkbox"/> ALT is normal (\leq upper limit of normal, ULN)	<input type="checkbox"/> INR is normal (≤ 1.3)	<input type="checkbox"/> Patient is asymptomatic		
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<input type="checkbox"/> Paracetamol concentration $< 10\text{mg/L}$ or below the treatment line on the nomogram	<input type="checkbox"/> ALT is normal (\leq upper limit of normal, ULN)	<input type="checkbox"/> INR is normal (≤ 1.3)	<input type="checkbox"/> Patient is asymptomatic								
 SNAP 12-hour acetylcysteine regimen 											
iii	Start acetylcysteine after admission blood results if any: <table border="0" style="width: 100%;"> <tr> <td style="width: 20%;"><input type="checkbox"/> Paracetamol concentration above the nomogram treatment line or greater than 10mg/L if therapeutic excess overdose pattern</td> <td style="width: 20%;"><input type="checkbox"/> ALT $>$ ULN (consider specialist advice if chronically elevated)</td> <td style="width: 20%;"><input type="checkbox"/> INR > 1.3 (consider specialist advice if chronically elevated)</td> <td style="width: 20%;"></td> </tr> </table>	<input type="checkbox"/> Paracetamol concentration above the nomogram treatment line or greater than 10mg/L if therapeutic excess overdose pattern	<input type="checkbox"/> ALT $>$ ULN (consider specialist advice if chronically elevated)	<input type="checkbox"/> INR > 1.3 (consider specialist advice if chronically elevated)							
<input type="checkbox"/> Paracetamol concentration above the nomogram treatment line or greater than 10mg/L if therapeutic excess overdose pattern	<input type="checkbox"/> ALT $>$ ULN (consider specialist advice if chronically elevated)	<input type="checkbox"/> INR > 1.3 (consider specialist advice if chronically elevated)									

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D	Drug reactions	Recognise: nausea, vomiting, flushing, urticarial rash, angioedema, tachycardia, wheeze.					
Consider taking the following actions:	<input type="checkbox"/> Temporarily stop the acetylcysteine infusion						
	<input type="checkbox"/> IV chlorphenamine 10 mg						
	<input type="checkbox"/> Restart the acetylcysteine infusion at a slower rate						
E	End of 2 nd infusion	At 12 hours, take bloods for paracetamol concentration, U&Es, LFTs, INR.					
	Continue acetylcysteine ^o if any:	Raised ALT >ULN	OR	ALT doubled or more from admission ($\geq 2 \times$ 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 (\leq ULN) AND ALT less than doubled since admission	&	Paracetamol concentration \leq 10mg/L	
	Medically fit for discharge if all:	INR increased by \leq 0.4 from admission	&	Normal ALT (\leq ULN) AND ALT less than doubled since admission	&	Paracetamol concentration \leq 10mg/L	

^oExtended 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:
 - ALT > 2 \times upper limit of normal (ULN),
 - ALT > ULN AND rising from the previous value AND doubled or more from admission,
 - ALT > ULN AND INR > 1.3 and rising in the absence of another cause,
 - Paracetamol concentration > 10 mg/L.
- Stop subsequent infusion bags (i.e., 5th bag or more) if blood results are normalising, i.e., either:
 - INR \leq 1.3, OR
 - INR $<$ 3.0 and falling on consecutive blood tests.

Acetylcysteine Blood Test Results						
Bloods	Baseline if available	Admission	End 2 nd bag (12 h)	4-hour repeat	End 3 rd bag	End 4 th bag
Date/time						
Paracetamol conc. (mg/L)						
ALT (IU/L)						
INR						
Urea (mmol/L)						
Creatinine (μ mol/L)						

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

See Trust Guidelines for detailed management of paracetamol overdose.

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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	
≥200	60	100	120	100	

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

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

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.

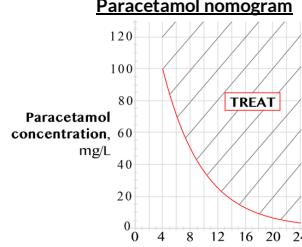
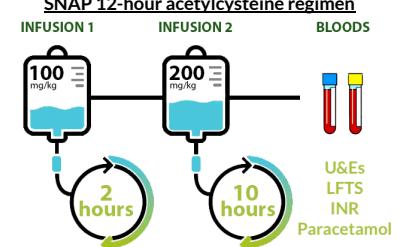
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Appendix 2. SNAP care pathway children under 6 years old.

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

MRN:
Name: addressograph
DOB:
Address:

1 Initial Evaluation		Sign	Date/Time			
Date of presentation: _____ / _____ / _____ Time at presentation: _____ : _____ Date of last ingestion: _____ / _____ / _____ Time at last ingestion: _____ : _____ Time since last ingestion: _____ hours <i>tick one:</i> <input type="checkbox"/> <8h <input type="checkbox"/> 8-24h <input type="checkbox"/> >24h <input type="checkbox"/> Unknown	Total overdose: _____ g Patient weight: _____ kg Overdose per weight: _____ mg/kg Pattern of ingestion (tick one if known): <input type="checkbox"/> Single acute overdose ($\geq 150\text{mg/kg}$ over a period 1 hour or less) <input type="checkbox"/> Staggered overdose ($\geq 75\text{mg/kg}$ over more than 1 hour AND deliberate self-harm) <input type="checkbox"/> Therapeutic excess ($\geq 75\text{mg/kg}$ over 24 hours OR licensed daily dose for ≥ 2 days)					
2 Management		Sign	Date/Time			
A Activated charcoal Dose: 1g/kg (max. 50g) Consider if all : <table border="1" style="margin-left: 20px; border-collapse: collapse;"> <tr> <td><input type="checkbox"/> Airway is protected</td> <td rowspan="3" style="width: 10%;"></td> </tr> <tr> <td><input type="checkbox"/> Presents within 1 hour</td> </tr> <tr> <td><input type="checkbox"/> Overdose $> 150\text{ mg/kg}$</td> </tr> </table>	<input type="checkbox"/> Airway is protected		<input type="checkbox"/> Presents within 1 hour	<input type="checkbox"/> Overdose $> 150\text{ mg/kg}$		
<input type="checkbox"/> Airway is protected						
<input type="checkbox"/> Presents within 1 hour						
<input type="checkbox"/> Overdose $> 150\text{ mg/kg}$						
B Blood 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: <ul style="list-style-type: none"> <input type="checkbox"/> Single acute overdose $> 150\text{mg/kg}$ & last ingestion over 8h ago <input type="checkbox"/> Single acute overdose $> 150\text{mg/kg}$ & unknown time of ingestion <input type="checkbox"/> Staggered overdose <input type="checkbox"/> Clinical features of liver toxicity (e.g. jaundice, liver tenderness) 						
ii Stop acetylcysteine after admission blood results if all: <ul style="list-style-type: none"> <input type="checkbox"/> Paracetamol concentration $< 10\text{mg/L}$ or below the treatment line on the nomogram <input type="checkbox"/> ALT is normal (\leq upper limit of normal, ULN) <input type="checkbox"/> INR is normal (≤ 1.3) <input type="checkbox"/> Patient is asymptomatic 						
 SNAP 12-hour acetylcysteine regimen 						
iii Start acetylcysteine after admission blood results if any: <ul style="list-style-type: none"> <input type="checkbox"/> Paracetamol concentration above the nomogram treatment line or greater than 10mg/L if therapeutic excess overdose pattern <input type="checkbox"/> ALT $>$ ULN (consider specialist advice if chronically elevated) <input type="checkbox"/> INR > 1.3 (consider specialist advice if chronically elevated) 						

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D	Drug reactions	Recognise: nausea, vomiting, flushing, urticarial rash, angioedema, tachycardia, wheeze.				
	Consider taking the following actions:	<p>Temporarily stop the acetylcysteine infusion</p> <p>IV chlorphenamine 2.5 mg (6 months to 5 years old)</p> <p>Restart the acetylcysteine infusion at a slower rate</p>				
E	End of 2 nd infusion	At 12 hours, take bloods for paracetamol concentration, U&Es, LFTs, INR.				
	Continue acetylcysteine ^o if any :	Raised ALT >ULN	OR	ALT doubled or more from admission ($\geq 2 \times$ 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 (\leq ULN) AND ALT less than doubled since admission	&	Paracetamol concentration \leq 10mg/L
	Medically fit for discharge if all :	INR increased by \leq 0.4 from admission	&	Normal ALT (\leq ULN) AND ALT less than doubled since admission	&	Paracetamol concentration \leq 10mg/L

^o **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:
 - ALT > 2 \times upper limit of normal (ULN),
 - ALT > ULN AND rising from the previous value AND doubled or more from admission,
 - ALT > ULN AND INR > 1.3 and rising in the absence of another cause,
 - Paracetamol concentration > 10 mg/L.
- Stop subsequent infusion bags (i.e., 5th bag or more) if blood results are normalising, i.e., either:
 - INR \leq 1.3, OR
 - INR < 3.0 and falling on consecutive blood tests.

Acetylcysteine Blood Test Results						
Bloods	Baseline if available	Admission	End 2 nd bag (12 h)	4-hour repeat	End 3 rd bag	End 4 th bag
Date/time						
Paracetamol conc. (mg/L)						
ALT (IU/L)						
INR						
Urea (mmol/L)						
Creatinine (μ mol/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 acetylcysteine 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		10-14
15-19	34	17		340	34	2 x 10mL acetylcysteine, 380mL diluent	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		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

NOTE: To ensure same infusion rate of 100 mL/hour for all weight bands, the same volume of 5%

This is different from current MHRA guidance which is to add the acetylcysteine volume to the

Notes/feedback	Feedback survey  https://forms.office.com/r/lJvGrXMfhTF

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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