

CORE TRAINING FOR DOCTORS

TIPS FROM THE SHOP FLOOR

Paracetamol overdose **C18**

Natasha Palipane, Estabrak Jiad,
Jacob F de Wolff

CLINICAL SKILLS FOR POSTGRADUATE EXAMINATIONS

Ascites **C23**

Selina J Chavda, Stuart L Bloom

WHAT YOU NEED TO KNOW ABOUT

Management of cirrhotic ascites **C28**

Maria Bashyam, Mario Lepore,
Marcus Harbord

COMING NEXT MONTH

TIPS FROM THE SHOP FLOOR

How to choose a suture

CLINICAL SKILLS FOR POSTGRADUATE EXAMINATIONS

Assessing the sense of smell

WHAT THEY DON'T TEACH YOU AT MEDICAL SCHOOL

Overview of pancreatic resections: indications and procedures

WHAT YOU NEED TO KNOW ABOUT

Hyposmia

Edited by Dr Daniel JB Marks, Academic Clinical Fellow in Translational Medicine, University College London and Dr Jacob de Wolff, Consultant Acute Physician, North West London Hospitals NHS Trust, Middlessex

Paracetamol overdose

Paracetamol overdose is a common acute medical presentation. Treatment protocols have changed substantially: in September 2012, the Medicines and Healthcare Products Regulatory Agency (2012a) issued a drug safety update on the treatment of paracetamol overdose with intravenous acetylcysteine. The simplified guidelines came after the Commission on Human Medicines carried out an evidence-based review following a number of reports where patients were not treated following paracetamol overdose as they were considered 'low risk', but nevertheless resulted in death or liver damage despite the patients having presented within 8–10 hours of overdose. The review identified that key determinants used in deciding whether or not to treat were either unreliable or derived from a weak evidence base. It also found strong evidence to suggest that, given within 8 hours of overdose, acetylcysteine is 'virtually 100% effective in preventing liver disease' (Medicines and Healthcare Products Regulatory Agency, 2012a); this formed the backbone of the updated guidelines.

Mechanisms of paracetamol toxicity

Paracetamol (N-acetyl-p-aminophenol, APAP, also called acetaminophen in the United States) is an effective and widely available analgesic and antipyretic. The mechanism of its analgesic properties is incompletely understood, but probably involves the inhibition of central and peripheral cyclooxygenase isoforms (Hinze and Brune, 2012).

Ms Natasha Palipane* is Medical Student, UCL Medical School, London, Dr Estabrak Jiad* is Senior House Officer in Stroke Medicine in the Department of Stroke Medicine, National Hospital for Neurology and Neurosurgery, London and Dr Jacob F de Wolff is Consultant Acute Physician in the Department of Acute Medicine, Northwick Park Hospital, Harrow, Middlesex HA1 3UJ

Correspondence to: Dr JF de Wolff
(jacobdewolff@nhs.net)

*These authors contributed to this work equally

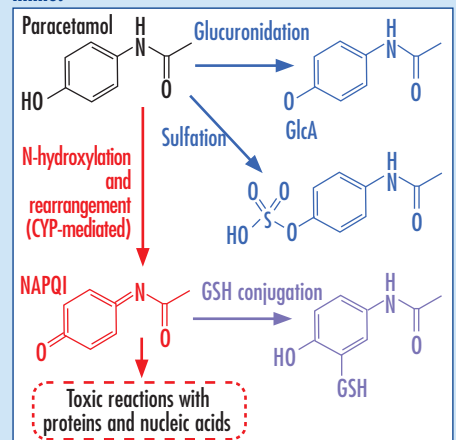
In recommended doses paracetamol is conjugated in the liver and the inactive metabolite is excreted by the kidneys (Figure 1). In excess it predominantly causes hepatic toxicity. This is mediated by saturation of the conjugating glucuronidase enzyme, forcing it to be metabolized by an alternative pathway consisting of cytochrome p450 isoenzymes. This alternative pathway results in the production of the toxic metabolite NAPQI (N-acetyl-p-benzoquinone imine), which is normally neutralized by glutathione in the liver. In paracetamol overdose NAPQI saturates glutathione resulting in cell necrosis that primarily affects the liver and (to a lesser extent) kidneys.

Although paracetamol reaches its maximum blood concentration within 30–60 minutes, acute liver failure usually follows after the first 24 hours and renal failure becomes evident around the third day. It is this delay in symptom manifestation that results in late presentation and previous ambiguity over treatment guidelines. Table 1 describes the signs and symptoms of acute paracetamol toxicity.

Management of paracetamol toxicity

Paracetamol toxicity is treated with activated charcoal and acetylcysteine. Activated charcoal acts to reduce paracetamol absorption, and acetylcysteine acts to replenish glutathione.

Figure 1. Metabolism of paracetamol. CYP = cytochrome p450; GlcA = glucuronic acid; GSH = glutathione; NAPQI = N-acetyl-p-benzoquinone imine.



ione stores. Activated charcoal is mainly effective if given within 1 hour of ingesting paracetamol, and its efficacy is greatly reduced thereafter (Ferner et al, 2011). Activated charcoal binds to the drug and reduces systemic absorption (Christopherson et al, 2002). It has only been tested on volunteers with non-toxic doses of paracetamol and the patient should be admitted with paracetamol levels measured 4 hours post ingestion and otherwise managed according to the guidelines (National Poisons Information Service, 2013). The guidelines do not recommend empirical treatment before availability of paracetamol levels.

A key consideration in the treatment plan is always the patient's wishes; this can be complicated by active suicidal thoughts and wishes to decline treatment.

How the guidelines have changed

The 2012 guidelines introduced a number of significant changes to the decision on whom to admit for acetylcysteine treatment and monitoring for toxicity. The changes are summarized in Table 2, and each will be discussed in turn.

Single treatment line protocol

It is not feasible to admit every patient with paracetamol overdose for observation

Table 1. Clinical features of paracetamol toxicity	
Symptoms	Nausea
	Vomiting
	Right upper quadrant pain
	Loss of coordination
	Sweating
	Trembling
Signs	Pallor
	Hypoglycaemia
	Encephalopathy
	Oliguria
Laboratory features	Abnormal liver function tests
	Alanine transaminase >1000 IU/litre
	Raised international normalized ratio >2
	Creatinine ≥150 µmol/litre
	Urea ≥6.7 mmol/litre

adapted from Hodgman and Garrard (2012)

and acetylcysteine infusion. If the time of overdose is known, the plasma paracetamol concentration measured after 4 hours post-ingestion is a strong predictor of toxicity. This is diagrammatically presented in the treatment nomogram (Figure 2). Acetylcysteine is administered if the plasma concentration at 4 hours lies on or above the 'treatment line' – the point above which there is a risk of toxicity and acetylcysteine is known to be of benefit. The original nomogram was formulated following a study of 30 patients (Prescott et al, 1971). This original nomogram had two separate treatment lines: a reduced line for patients with pre-existing risk factors for liver disease (Table 3) who ought to be treated if their 4-hour concentration reached ≥100 mg/litre and the other for patients without risk factors who were to be treated if 4-hour concentrations reached ≥200 mg/litre. One of the key changes following the 2012 review is removal of the need to assess for risk factors resulting in a

Table 2. Guidance on intravenous acetylcysteine administration

Single treatment line nomogram regardless of risk factors for liver damage

Increased infusion time of 60 minutes for loading dose

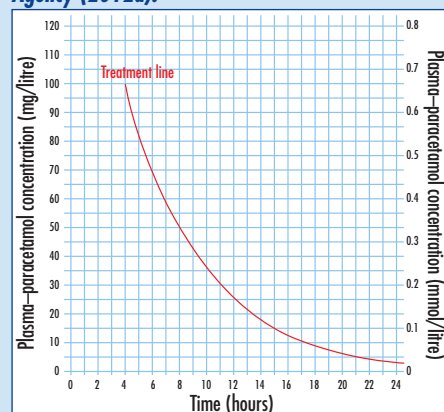
Weight-based dosing tables acetylcysteine administration

Eradication of acetylcysteine hypersensitivity as a contraindication

Administration of acetylcysteine without delay when there is doubt over timing of ingestion or staggered overdose

From Medicines and Healthcare Products Regulatory Agency (2012c)

Figure 2. Single line treatment nomogram. From Medicines and Healthcare Products Regulatory Agency (2012a).



single line treatment nomogram for all patients presenting with paracetamol overdose (Figure 2).

The new nomogram was introduced following evidence that clinical determination of the risk factors is both difficult and imprecise. As well as lacking the tools that confidently assess risk, there have been a number of cases where treatment according to the normal low-risk treatment line had resulted in fatal liver failure as these patients presented with levels <200 mg/litre on 4-hour readings (Bridger et al, 1998). On the other hand, it has been argued that lowering the treatment line from 200 mg/litre would prevent only a very small number of liver unit admissions after paracetamol overdose (Beer et al, 2007).

In 2012 the Medicines and Healthcare Products Regulatory Agency (2012a) felt that it had received reports of too many fatal cases of patients being refused acetylcysteine as result of risk profiling, which drove them to adopt a more vigilant approach with a single treatment line nomogram.

The 4-hour paracetamol level can be unreliable if the time of ingestion is not known, and if the patient took medication that delays gastric emptying (e.g. opioids or antihistamines with anticholinergic properties). In this case, levels below the treatment line may still warrant full course acetylcysteine treatment and observation (Ferner et al, 2011).

Infusion rate

Acetylcysteine is administered with 5% glucose as three doses. Where the loading dose used to have an infusion rate of 15 minutes, this has now increased to

Table 3. Risk factors influencing the original high-risk treatment line

Pre-existing liver disease
Reduced food intake
Chronic alcohol abuse
Long-term use of enzyme-inducing drugs
Conditions reducing glutathione levels, e.g. cystic fibrosis, hepatitis C, AIDS
Opioid co-ingestion
Age
Smoking

From Ferner et al (2011)

Table 4. Adult dosage table

Adult acetylcysteine prescription (each ampoule = 200 mg/ml acetylcysteine). Please circle appropriate weight and volume

Regimen	First infusion		Second infusion		Third infusion	
Infusion fluid	200 ml 5% glucose or sodium chloride 0.9%		500 ml 5% glucose or sodium chloride 0.9%		1000 ml 5% glucose or sodium chloride 0.9%	
Duration of infusion	1 hour		4 hours		16 hours	
Drug dose	150 mg/kg acetylcysteine		50 mg/kg acetylcysteine		100 mg/kg acetylcysteine	
Patient weight* (kg)	Ampoule vol.† (ml)	Infusion rate (ml/h)	Ampoule vol.† (ml)	Infusion rate (ml/h)	Ampoule vol.† (ml)	Infusion rate (ml/h)
40–49	34	234	12	128	23	64
50–59	42	242	14	129	28	64
60–69	49	249	17	129	33	65
70–79	57	257	19	130	38	65
80–89	64	264	22	131	43	65
90–99	72	272	24	131	48	66
100–109	79	279	27	132	53	66
≥110	83	283	28	132	55	66

* Dose calculations are based on the weight in the middle of each band. If the patient weighs less than 40 kg use the paediatric dosage table. † Ampoule volume has been rounded up to the nearest whole number. From Medicines and Healthcare Products Regulatory Agency (2012b)

Table 5. Paediatric dosage table

Paediatric acetylcysteine prescription (each ampoule = 200 mg/ml acetylcysteine). Please circle appropriate weight and volume

Regimen	First infusion		Second infusion		Third infusion	
Infusion	50 mg/ml for 1 hour		6.25 mg/ml for 4 hours		6.25 mg/ml for 16 hours	
Infusion rate	3 ml/kg/h		2 ml/kg/h		1 ml/kg/h	
Patient weight (kg)	Total infusion vol. (ml)	Infusion rate (ml/h)	Total infusion vol. (ml)	Infusion rate (ml/h)	Total infusion vol. (ml)	Infusion rate (ml/h)
1	3	3	8	2	16	1
2	6	6	16	4	32	2
3	9	9	24	6	48	3
4	12	12	32	8	64	4
5	15	15	40	10	80	5
6	18	18	48	12	96	6
7	21	21	56	14	112	7
8	24	24	64	16	128	8
9	27	27	72	18	144	9
10–14	38	38	100	24	208	13
15–19	53	53	140	35	288	18
20–24	68	68	180	45	368	23
25–29	83	83	220	55	448	28
30–34	98	98	260	65	528	33
35–39	113	113	300	75	608	38

* Dose calculations are based on the weight in the middle of each band. If the patient weighs more than 40 kg use the adult dosage table. Figures have been rounded up to the nearest whole number. From Medicines and Healthcare Products Regulatory Agency (2012b)

60 minutes. This follows studies which have shown that efficacy of acetylcysteine following a 60-minute infusion is equivalent to that following a 15-minute infusion (Kerr et al, 2005), and evidence showing that the majority of adverse reactions, including anaphylactoid reactions, occur within the first hour. This is thought to be the result of a dose–response relationship where peak acetylcysteine levels are reached during loading infusion causing activation of inflammatory mediators. By prolonging the loading infusion, the incidence of these reactions can be reduced, enabling the continuation of N-acetyl cysteine infusion (Lynch and Robertson, 2004).

Dosing tables

The reviewed guidelines propose pre-calculated weight-based dosage tables (Tables 4 and 5) for intravenous dosing with the intention of reducing calculation errors, a considerable number of which have led to further injury (Hayes et al, 2008).

Hypersensitivity

Adverse reactions to acetylcysteine occur in 20–50% of patients (Sandilands and Bateman, 2009). Most commonly, these consist of nausea and vomiting, but there may also be features similar to anaphylaxis including flushing, pruritus, rash, angioedema, bronchospasm and hypotension. These reactions are incompletely understood but involve non-mast cell-mediated histamine release and thus are not true anaphylactic reactions (Yamamoto et al, 2014). Adverse reactions are more common in those who present with lower paracetamol levels (Sandilands and Bateman, 2009). As discussed above, slower infusion of the first dose is expected to reduce the incidence of these reactions.

Anaphylactoid cutaneous reactions are usually mild, and treatment should be with antihistamines and temporarily stopping the infusion. Importantly, further treatment with acetylcysteine is not contraindicated as this is not an ‘allergy’, and should be reinitiated as soon as possible, ideally within an hour and at a slower rate. Inhaled β_2 -agonists can be used to alleviate bronchospasm and antiemetics for nausea and vomiting. Steroids are unnecessary and should not be used (National Poisons Information Service, 2013; Yamamoto et al, 2014).

Staggered overdose

A staggered paracetamol overdose is defined as ingestion of a potentially toxic dose of paracetamol over more than an hour. The Commission on Human Medicines does not provide a numerical definition for toxic dose.

Staggered overdoses present a challenge in clinical practice and are associated with higher mortality rates (Craig et al, 2012). Often, laboratory paracetamol levels will be within the therapeutic range of 10–15 mg/litre (Dargan et al, 2001). Clearly the nomogram is not useful in this scenario as it is designed for paracetamol overdoses taken in one sitting, but an accurate history of the extent of abuse is still required to guide future management decisions.

Doses of greater than 150 mg/kg/24 h are likely to cause serious toxicity. Any patient presenting with signs of liver damage (*Table 1*) should be treated immediately with acetylcysteine regardless of the plasma paracetamol levels. Doses between 75–150 mg/kg rarely cause toxicity (National Poisons Information Service, 2013) but individual factors (*Table 3*) are thought to play a significant role and thus the Commission on Human Medicines has recommended treatment with acetylcysteine for all staggered overdoses. Patients presenting with no features of acute liver toxicity more than 24 hours after last ingestion of paracetamol are unlikely to have taken a significant overdose and the decision to treat should be made in conjunction with clinical judgement (National Poisons Information Service, 2013).

In any case where there is doubt, treatment with acetylcysteine should be started with monitoring for signs of toxicity (National Poisons Information Service, 2013).

Late presentation

Acetylcysteine is most effective when administered within 8 hours of overdose, but some patients will present after this. Late presenters can be split into those presenting between 8 and 24 hours and those presenting more than 24 hours after an acute overdose.

8–24 hours post ingestion

Because the efficacy of acetylcysteine falls sharply after 8 hours, those who present between 8 and 24 hours who are thought to have taken a significant acute overdose

(>150 mg/kg) should be commenced on acetylcysteine immediately without waiting for blood results. Blood should be tested urgently for paracetamol levels, urea and electrolytes including creatinine, liver function tests, international normalized ratio, full blood count and bicarbonate. Risk of significant toxicity should be reassessed using the nomogram when blood results are available. Regardless of paracetamol levels, any evidence of liver injury should prompt continuation of the acetylcysteine infusion (National Poisons Information Service, 2013).

>24 hours post ingestion

Current guidelines state that treatment should be initiated immediately in any person who has taken an overdose presenting with signs of liver failure. In those presenting more than 24 hours after acute ingestion with no signs of liver failure, a short delay while waiting for blood results should not lead to any harm. Any of the laboratory parameters in *Table 1* or a detectable paracetamol level suggests a significant overdose and treatment with acetylcysteine should be commenced. Repeat blood tests should be taken at 8–16-hour intervals and the acetylcysteine infusion can be stopped when the international normalized ratio is less than 1.3 (National Poisons Information Service, 2013).

If the patient is asymptomatic, the plasma paracetamol level is undetectable, the alanine transferase is less than twice the upper limit and the international normalized ratio is less than 1.3 with a normal plasma creatinine level then the patient can be discharged safely with advice to return if any new symptoms develop (National Poisons Information Service, 2013). The authors recommend an assessment of suicidal risk before discharge.

Mehrpour et al (2011) showed evidence that high-dose intravenous N-acetylcysteine can lead to a substantial improvement even in those with delayed presentation but there is also some evidence that prolonged acetylcysteine infusions can result in an impaired ability of the liver to undergo self regeneration (Athuraliya and Jones, 2009).

Challenging intravenous access

In those in whom intravenous access cannot be obtained, acetylcysteine can be administered orally (although at present

this is an unlicensed preparation in the UK). However, vomiting accompanies significant paracetamol overdoses, limiting the use of the oral route. Furthermore, nausea and vomiting is more common as a side effect when administering acetylcysteine orally although the risk of anaphylactoid reactions is lower (Bebarta et al, 2010).

A loading dose of 140 mg/kg given orally as a 5% solution using the intravenous preparation, with further maintenance doses at 70 mg/kg as a 5% solution every 4 hours to a total of 1330 mg/kg over 72 hours, is used to treat overdoses in the absence of intravenous access. The intravenous preparation may be diluted with water or juice if only a higher concentration is available (Joint Formulary Committee, 2013).

Efficacy of the oral route has been shown to be as effective as the intravenous route when treatment is initiated within 8 hours of overdose (Williamson et al, 2013). Patients treated using the oral route averaged a longer hospital stay (7 days *vs* 4 days) than those treated via the intravenous route and thus the costs were higher (Martello et al, 2010).

A 2006 Cochrane review (Brok et al, 2006) concluded that there is no evidence for the superiority of acetylcysteine over methionine and referenced observational studies that concluded that there was no statistical difference between acetylcysteine and methionine but that an increased number of adverse events were noted in the patients treated with methionine. The Cochrane review recognizes that the study data are small and there are considerable risks of bias from comparison groups which were treated 3–10 years earlier. At present there is emerging research on the possible role of using methionine as an alternative to acetylcysteine, but this is still in its early stages (Brown et al, 2012).

The use of methionine must be discussed with the National Poisons Agency before it is prescribed. For adults, it is usually given at a dose of 2.5 g four times a day, for a maximum of four doses and must be administered within 10–12 hours of overdose. In January 2013 the product licence for methionine was relinquished by PharmaNord and it is currently unavailable in the UK (National Poisons Information Service, 2013).

Conclusions

This article has outlined the updated guidelines from the Medicines and Healthcare Products Regulatory Agency (2012a) regarding paracetamol overdoses. This is the commonest type of overdose in the UK. The introduction of a single risk nomogram forms the backbone of the guidance, which was introduced as a result of a number of adverse events from patients not being treated as they were perceived to be 'low risk'. Assessment of individual risk factors as a means of withholding acetylcysteine no longer has a place in acute clinical practice. Acetylcysteine provides the mainstay of treatment for paracetamol overdose which acts to replenish glutathione stores. It is most effective less than 8 hours after an acute overdose but has a role in late presenters (>8 hours) and staggered overdoses.

The rate of infusion of the first bag has been increased from 15 minutes to over 1 hour to reduce the incidence of anaphylactoid reactions. Anaphylactoid reactions are histamine mediated and do not preclude further treatment with acetylcysteine as these are not true anaphylactic reactions. **BJHM**

Figure 1 is reproduced courtesy of Mr Filipe Vasconcellos, Language Solutions, São Paulo, Brazil.

Conflict of interest: none. Dr JF de Wolff is section editor of British Journal of Hospital Medicine. He took no part in the peer review process nor in the decision to accept this for publication.

Athuraliya TN, Jones AL (2009) Prolonged N-acetylcysteine therapy in late acetaminophen poisoning associated with acute liver failure--a need to be more cautious? *Crit Care* **13**(3): 144 (doi: 10.1186/cc7800)

Bebarta VS, Kao L, Froberg B et al (2010) A multicenter comparison of the safety of oral versus intravenous acetylcysteine for treatment of

- acetaminophen overdose. *Clin Toxicol (Phila)* **48**(5): 424–30 (doi: 10.3109/15563650.2010.486381)
- Beer C, Pakraven N, Hudson M, Smith LT, Simpson K, Bateman DN, Thomas SHL (2007) Liver unit admission following paracetamol overdose with concentrations below current UK treatment thresholds. *QJM* **100**(2): 93–6
- Bridger S, Henderson K, Glucksman E, Ellis AJ, Henry JA, Williams R (1998) Deaths from low dose paracetamol poisoning. *BMJ* **316**: 1724–5
- Brok J, Buckley N, Gluud C (2006) Interventions for paracetamol (acetaminophen) overdose. *Cochrane Database Syst Rev* **2**: CD003328
- Brown JM, Ball JG, Wright MS, Van Meter S, Valentovic MA (2012) Novel protective mechanisms for S-adenosyl-L-methionine against acetaminophen hepatotoxicity: improvement of key antioxidant enzymatic function. *Toxicol Lett* **212**(3): 320–8 (doi: 10.1016/j.toxlet.2012.05.018)
- Christophersen AB, Levin D, Hoegberg LC, Angelo HR, Kampmann JP (2002) Activated charcoal alone or after gastric lavage: a simulated large paracetamol intoxication. *Br J Clin Pharmacol* **53**(3): 312–17
- Craig DG, Bates CM, Davidson JS, Martin KG, Hayes PC, Simpson KJ (2012) Staggered overdose pattern and delay to hospital presentation are associated with adverse outcomes following paracetamol-induced hepatotoxicity. *Br J Clin Pharmacol* **73**(2): 285–94 (doi: 10.1111/j.1365-2125.2011.04067.x)
- Dargan PI, Ladhani S, Jones AL (2001) Measuring plasma paracetamol concentrations in all patients with drug overdose or altered consciousness: does it change outcome? *Emerg Med J* **18**(3): 178–82
- Ferner RE, Dear JW, Bateman DN (2011) Management of paracetamol poisoning. *BMJ* **342**: d2218 (doi: 10.1136/bmj.d2218)
- Hayes BD, Klein-Schwartz W, Doyon S (2008) Frequency of medication errors with intravenous acetylcysteine for acetaminophen overdose. *Ann Pharmacother* **42**(6): 766–70 (doi: 10.1345/aph.1K685)
- Hinz B, Brune K (2012) Paracetamol and cyclooxygenase inhibition: is there a cause for concern? *Ann Rheum Dis* **71**(1): 20–5 (doi: 10.1136/ard.2011.200087)
- Hodgman MJ, Garrard AR (2012) A review of acetaminophen poisoning. *Crit Care Clin* **28**(4): 499–516 (doi: 10.1016/j.ccc.2012.07.006)
- Joint Formulary Committee (2013) *British National Formulary*. 65th edn. British Medical Association and Royal Pharmaceutical Society of Great Britain, London
- Kerr F, Dawson A, Whyte IM et al (2005) The Australasian Clinical Toxicology Investigators Collaboration randomized trial of different loading infusion rates of N-acetylcysteine. *Ann Emerg Med* **45**(4): 402–8
- Lynch RM, Robertson R (2004) Anaphylactoid reactions to intravenous N-acetylcysteine: a prospective case controlled study. *Accid Emerg Nurs* **12**(1): 10–15
- Martello JL, Pummer TL, Krenzlok EP (2010) Cost minimization analysis comparing enteral N-acetylcysteine to intravenous acetylcysteine in the management of acute acetaminophen toxicity. *Clin Toxicol (Phila)* **48**(1): 79–83 (doi: 10.3109/15563650903409799)
- Medicines and Healthcare Products Regulatory Agency (2012a) Paracetamol overdose: new guidance on treatment with intravenous acetylcysteine. www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON185624 (accessed 28 May 2014)
- Medicines and Healthcare Products Regulatory Agency (2012b) Acetylcysteine 200mg/ml injection for infusion administration information for the healthcare professional. www.mhra.gov.uk/home/groups/pl-p/documents/drugsafetymessage/con178226.pdf (accessed 28 May 2014)
- Medicines and Healthcare Products Regulatory Agency (2012c) Paracetamol overdose: Simplification of the use of intravenous acetylcysteine. www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON178225 (accessed 28 January 2015)
- Mehrpour O, Shadnia S, Sanaei-Zadeh H (2011) Late extensive intravenous administration of N-acetylcysteine can reverse hepatic failure in acetaminophen overdose. *Hum Exp Toxicol* **30**(1): 51–4 (doi: 10.1177/0960327110366182)
- National Poisons Information Service (2013) TOXBASE - paracetamol index (UK and Ireland). www.toxbase.org/Chemicals/Management-Pages/Paracetamol-Index-UK/ (accessed 28 May 2014)
- Prescott LF, Roscoe P, Wright N, Brown S (1971) Plasma paracetamol half-life and hepatic necrosis in patients with paracetamol overdosage. *Lancet* **i**: 519–22
- Sandilands EA, Bateman DN (2009) Adverse reactions associated with acetylcysteine. *Clin Toxicol (Phila)* **47**(2): 81–8 (doi: 10.1080/15563650802665587)
- Williamson K, Wahl MS, Mycyk MB (2013) Direct comparison of 20-hour IV, 36-hour oral, and 72-hour oral acetylcysteine for treatment of acute acetaminophen poisoning. *Am J Ther* **20**(1): 37–40 (doi: 10.1097/MJT.0b013e318250f829)
- Yamamoto T, Spencer T, Dargan PI, Wood DM (2014) Incidence and management of N-acetylcysteine-related anaphylactoid reactions during the management of acute paracetamol overdose. *Eur J Emerg Med* **21**(1): 57–60 (doi: 10.1097/MEJ.0b013e328364eb22)

TOP TIPS

- An accurate history of the amount and the timing of the paracetamol ingested is crucial.
- Paracetamol levels should be measured after at least 4 hours of the overdose.
- The infusion rate of the first bag of acetylcysteine has increased to 1 hour.
- Acetylcysteine hypersensitivity reactions can often be managed by slowing down the rate of infusion.
- All patients should have an assessment of suicidal risk before discharge.

KEY POINTS

- There is now just one single treatment line involved in the nomogram for treating paracetamol overdose with acetylcysteine.
- The infusion rate of has been increased from 15 minutes to 60 minutes to reduce the risk of adverse drug reactions.
- Dosing tables based on weight have now replaced the need to calculate required doses.
- A late presenter with signs of liver failure should be commenced on acetylcysteine immediately rather than waiting for blood paracetamol level results to arrive
- The nomogram is unreliable in staggered overdoses. In these cases, all patients should be treated with acetylcysteine.