Trainees Section

Problem-Based Review: Paracetamol Overdose

Key Messages
- ingestion of >250mg/kg or >12g total paracetamol carries a high risk of significant hepatotoxicity
- acute alcohol intake may be protective against paracetamol-induced liver damage
- alcoholics are at particularly high risk of hepatotoxicity following repeated supratherapeutic ingestion (RSTI) of paracetamol
- gastrointestinal decontamination with 50g oral activated charcoal should be considered if presentation is within 1h of ingestion of a potentially significant amount of paracetamol
- the need for treatment with N-acetylcysteine (NAC) is determined by using the Prescott nomogram when time of ingestion is known
- the efficacy of NAC declines rapidly after 8h from ingestion
- temporary discontinuation of the infusion and/or antihistamine is usually all that is required following an anaphylactoid reaction to NAC
- NAC itself may cause a rise in INR up to 1.3 by destabilization of clotting factors
- consider repeating the paracetamol level after treatment with NAC in cases of massive overdose or co-ingestion of drugs associated with delayed gastric emptying and continue the NAC infusion beyond 20h if still elevated
- King's College criteria and arterial lactate may be used to guide referral to a liver unit
- following staggered paracetamol overdose or RSTI, treatment with NAC is indicated if raised ALT/INR, paracetamol level >20mg/l or ingestion of >150mg/kg in 24h (>75mg/kg in 24h if high risk)

Case Vignette

A 29-year old male presents to the emergency department 1h after an overdose of cocodamol. He admits to taking approximately 60 x 8/500mg tablets, with alcohol, over a 20 minute period. He has a past history of depression, treated by his GP with citalopram 20mg OD. He has no previous history of deliberate self-harm. His past medical history is otherwise unremarkable and he is not on any additional medications. He drinks approximately 40 units of alcohol per week. Physical examination is unremarkable, his pupils are normal diameter and his Glasgow Coma Scale is 15. He weighs 82kg.

How would you determine his risk of hepatotoxicity from the paracetamol ingestion?

He has ingested 60 x 500 = 30g of paracetamol = 30,000/82 = 366mg/kg. Following acute paracetamol overdose, hepatotoxicity is unlikely with ingestions <150mg/kg but likely with ingestions >250mg/kg, and any ingestion >12g is potentially fatal.[1] Acute co-ingestion of alcohol may actually confer a limited degree of hepatoprotection as ethanol inhibits CYP2E1, the cytochrome p450 enzyme responsible for metabolizing paracetamol to its toxic metabolite *N*-acetyl-*p*-benzoquinoneimine (NAPQI).[2] The relationship between chronic alcohol consumption and risk of paracetamol toxicity is complex and still debated. Chronic alcohol abuse induces CYP2E1 levels and depletes hepatic glutathione stores,[3] potentially increasing the risk of paracetamol induced hepatotoxicity. However, several retrospective studies have concluded that patients with a history of excessive alcohol intake are not at increased risk of hepatotoxicity or a worse prognosis following a *single acute* overdose of paracetamol.[4,5] Alcoholics do not appear to be at increased risk of hepatotoxicity when using paracetamol at recommended therapeutic doses either[6] but they are at high risk of liver toxicity following repeated supratherapeutic (6-8g/day) ingestions of paracetamol.[7] According to current guidance,[1] our patient should be considered at high risk of hepatotoxicty as he 'regularly consumes alcohol in excess of recommended amounts'. Other high risk factors for hepatotoxicity (which do not apply to the patient in question) include malnutrition (e.g. starvation during febrile illness, eating disorders, AIDS, hepatitis C) and hepatic enzyme induction (e.g. carbamazepine, phenytoin, rifampicin, St. John's wort, antiretrovirals).[1]

What initial management steps are required?

He has presented within 1h of a potentially life-threatening ingestion of paracetamol and should therefore receive gastrointestinal decontamination with 50g of oral activated charcoal.[1] In most

Dr Tom Heaps
Consultant in Acute Medicine
University Hospitals Coventry and Warwickshire
Email: tom.heaps@uhcw.bhs.uk

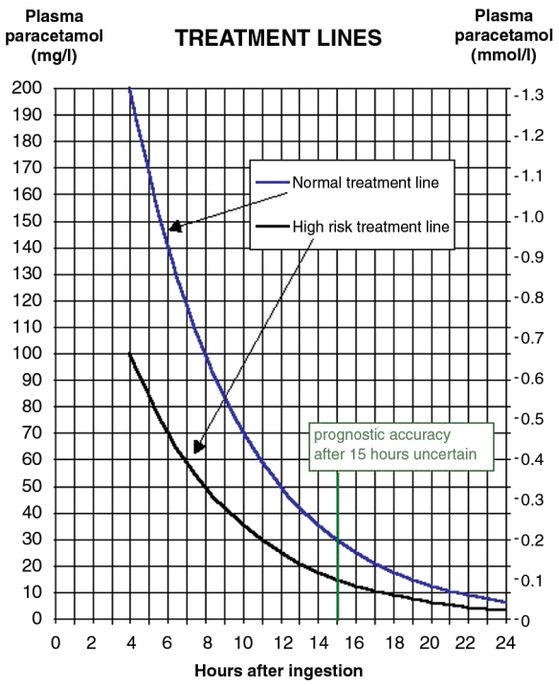

Figure 1. Prescott nomogram used to determine need for treatment with NAC after paracetamol overdose.

instances, paracetamol absorption is maximal at 4h post-ingestion.[8] He should therefore have his paracetamol levels checked 3h after admission (i.e. at 4h post-ingestion) together with baseline bloods for LFT, U&E, INR and a bicarbonate.[1] An arterial blood gas (ABG) should be obtained if he was drowsy or appeared unwell to assess for respiratory failure and lactic acidosis. There is no need to check salicylate levels routinely in poisoned patients in the absence of a history of aspirin ingestion, raised anion gap metabolic acidosis and clinical features of salicylism.[9] If his GCS was reduced with small pupils he should receive IV naloxone to counter the effects of the codeine component of the ingested cocodamol.

His paracetamol level at 4h should be plotted on the standard Prescott treatment nomogram (Figure 1) to determine the need for treatment with *N*-acetylcysteine. This nomogram was devised from retrospective data in a small cohort of 57 patients[10] but has stood the test of time with a very small incidence of significant hepatotoxicity (2% in one study[11]) in patients whose paracetamol levels are below the treatment line (provided the history with respect to timing is correct and patients with risk factors are correctly identified as being at high risk). Treatment with NAC should be initiated within 8h wherever possible as its efficacy declines rapidly from 8h post-ingestion.[12] It is therefore recommended that NAC is started immediately in patients who present after 8h with a history of ingestion of >150mg/kg; treatment can later be discontinued if a subsequent paracetamol level is below the appropriate treatment line.[1]

His 4h paracetamol level returns at 374mg/l (i.e. well above the high risk treatment line which begins at 100mg/l at 4h). Other baseline bloods are unremarkable. He is started on a standard regimen of IV N-acetylcysteine; 150mg/kg in 200ml 5% dextrose over 15min followed by 50mg/kg in 500ml 5% dextrose over 4h and then 100mg/kg in 1000ml 5% dextrose over 16h. 20 minutes after the NAC infusion is commenced, he complains of feeling unwell and begins vomiting. He appears flushed with a generalized urticarial rash and is dyspnoeic with widespread wheeze on chest auscultation. His blood pressure is 132/76.

What is the most likely cause of his symptoms and how would you manage them?

His symptoms most likely represent an adverse reaction to the NAC infusion. Adverse reactions to NAC are common occurring in between 5-56% of patients, depending on definitions used and whether the study was prospective or retrospective.[13] Nausea, vomiting, flushing, generalized erythema and itching are common reactions, whilst urticaria, angioedema, bronchospasm and hypotension are less commonly observed. Such reactions are thought to be anaphylactoid in nature i.e. the release of histamine is involved but this is not immune/IgE-mediated and prior exposure to NAC is not a pre-requisite. The risk of anaphylactoid reactions is concentration dependent (i.e. more likely during or just after the initial 15 minute infusion of NAC)[14] and is increased in females, atopic individuals and those with low serum paracetamol levels.[13] In general, temporary discontinuation of the NAC infusion is all that is required.[1] In more severe cases, IV antihistamines and nebulized bronchodilators may be required.[14] There is no role for corticosteroids as the reaction is not immune-mediated. Even after a severe reaction, NAC infusion can usually be restarted at 50mg/kg over 4h without further problems.[15]

After IV chlorpheniramine and nebulized salbutamol, the patient completed the remainder of his NAC infusion uneventfully. He is still complaining of feeling nauseous and has mild right upper quadrant tenderness. His blood tests are repeated at the end of the infusion. His ALT, INR, bicarbonate and U&Es are all within normal limits.

Is he now medically fit to be discharged?

In the majority of cases, if the ALT, INR, bicarbonate and U&Es are normal at the end of the 20.25h course of IV NAC, the patient can be safely discharged with advice to return to hospital if vomiting or abdominal pain occur.[1] However, there have been several recent reports highlighting the potential for significant hepatotoxicity to occur despite initiation of NAC within 8h of ingestion and normal ALT/INR values after completion of the NAC infusion.[16-18] The common features in these cases were that massive quantities of paracetamol had been ingested (solubility of paracetamol may have been exceeded) and/or drugs known to delay gastric emptying were co-ingested with paracetamol

which resulted in significantly delayed absorption and late hepatotoxicity. The patient in our case has ingested a large quantity of paracetamol, his 4h paracetamol levels were significantly elevated, he has also ingested co-codamol (codeine and other opiates delay gastric emptying and reduce GI motility) and is symptomatic at the end of the NAC infusion. A pragmatic approach in cases of massive paracetamol ingestion and/or co-ingestion of drugs associated with delayed gastric emptying is to repeat the paracetamol level at the end of the 20.25h course of NAC and continue the infusion of NAC if this is still elevated.[19]

If his ALT and/or INR were elevated following NAC treatment how would you proceed?

NAC itself (and high plasma concentrations of paracetamol) can, in the absence of hepatotoxicity, cause minor elevations in INR due to inhibition of activation of vitamin K-dependent clotting factors VII and IX.[20] Therefore, if the INR has risen to ≤1.3 following NAC *and* ALT is <150 *and* <2x the admission ALT value, no further treatment is required and the patient may be discharged.[1] If the INR is ≤1.3 but the ALT has risen to >150 or is >2x the admission ALT value, current advice is to continue NAC treatment at 100mg/kg in 1000ml 5% dextrose over 16h (or 150mg/kg in 1000ml 5% dextrose over 24h) with repeat bloods every 12h.[21] Similarly, NAC infusion should be continued if both the ALT and INR are elevated at the end of the initial course of treatment.[1] NAC may be stopped and the patient discharged once INR <2 and ALT <50% of peak value (or decreasing with 3 serial measurements <1000).[22]

What are the criteria for liver transplantation following paracetamol overdose?

The King's College Criteria for liver transplantation following paracetamol overdose (see box 1) are the most widely used and validated.[23] Without transplantation, survival in patients meeting these criteria is usually <20%.[24] Arterial lactate >3.5 mmol/l 4 h after adequate fluid resuscitation or >3.0 mmol/l 12h after adequate fluid resuscitation are also sensitive and specific predictors of death without transplant.[25] Continued infusion of NAC in patients with paracetamol-induced hepatic failure has been shown to reduce cerebral oedema, need for dialysis and cardiovascular complications and to improve survival, probably by a variety of immunomodulatory, haemodynamic and oxygen free radical-scavenging mechanisms.[26]

- arterial lactate >3.5mmol/l 4h after adequate fluid resuscitation

or

- arterial pH <7.3 (or arterial lactate >3.0mmol/l) 12h after adequate fluid resuscitation

or all 3 of the following at any time:

- PT > 100s (INR >6.7)
- creatinine>300µmol/l
- grade III or IV encephalopathy

Box 1. Modified King's College Criteria for liver transplantation following paracetamol overdose.

How would his management have changed if he had taken a staggered overdose or presented with repeated supratherapeutic ingestions (RSTI) of paracetamol?

Following a staggered overdose or RSTI, plasma paracetamol concentrations are not reliable and should not be plotted on the nomogram to determine need for NAC. An elevated paracetamol level helps to confirm ingestion and indicates that there is remaining paracetamol which is yet to be metabolized. There is no real evidence base to guide treatment following staggered overdose or RSTI. Treatment with NAC should be commenced if evidence of hepatotoxicity (raised ALT and/or INR) at presentation.[21] Otherwise, TOXBASE® suggests treatment with NAC if >150mg/kg of paracetamol (>75mg/kg in patients with risk factors) has been ingested in a 24h period.[1] Others[27] have suggested considering treatment with NAC following a staggered overdose or RSTI of paracetamol if:

a. >10g or >200mg/kg ingested over a single 24h period
b. >6g or >150 mg/kg per 24h period for ≥48h hours or longer
c. >4g or >100mg/kg per day if high risk for paracetamol toxicity

If the INR and ALT are normal 24h after the last ingestion and the patient is asymptomatic, significant toxicity is unlikely and NAC can be discontinued.[1] Indications for continuing NAC beyond the initial 20.25h course are the same as for acute paracetamol overdose.

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