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Guidelines for the management of Paracetamol Poisoning

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ABSTRACT : *Paracetamol is the most widely used over-the-counter analgesic agent in the world. It is involved in a large proportion of accidental paediatric exposures and deliberate selfpoisoning cases and is the leading pharmaceutical agent. Paracetamol is also the single most commonly taken drug in overdoses that lead to hospital presentation and admission. Hepatic failure and death are uncommon outcomes, although paracetamol remains the most important single cause of acute fulminant hepatic failure.*

Acute deliberate self-poisoning, accidental paediatric exposure and inadvertent repeated supratherapeutic ingestions all require specific approaches to risk assessmen and manage-ment. This guideline details management for paracetamol poisoning in all these situations

Key Words: *Pharmacokinetics,Gastrointestinal Decontamination,Acetyl Cysteine*

Paracetamol is rapidly absorbed from the small intestine. In therapeutic doses, peak serum concentrations occur within 1–2 hours for standard tablet or capsule formulations and within 30 minutes for liquid preparations. Peak serum concentrations after therapeutic doses do not usually exceed 20 mg/L (132 ⌈mol/L).Twenty per cent of the ingested dose undergoes first-pass metabolism in the gut wall sulphation). Distribution is usually within 4 hours of ingestion for standard preparations and 2 hours for liquid preparations. Volume of distribution is 0.9 L/kg. Further elimination occurs by hepatic biotransformation. After therapeutic doses, the elimination half-life is 1.5–3 hours. About 90% is metabolised to inactive sulphate and glucuronide conjugates that are excreted in the urine. Metabolism of the remainder is via cytochrome P450 (chiefly 2E1 and 3A4) and results in the highly reactive intermediary compound *N*-acetyl-*p*-benzoquinone imine (NAPQI). In normal conditions, NAPQI is immediately bound by intracellular glutathione and eliminated in the urine as mercapturic adducts.

With increased paracetamol doses, greater production of NAPQI may deplete glutathione stores. When glutathione depletion reaches a critical level (thought to be about 30% of normal stores), NAPQI binds to other proteins, causing damage to the hepatocyte. Glutathione depletion itself may also be injurious.

Management of paracetamol overdose

Gastrointestinal decontamination

Significant hepatic injury is extremely rare after acute single accidental paracetamol

ingestion in children under 6 years of age, and it is very uncommon for them to have concentrations that require acetylcysteine treatment. Therefore, in children under 6 years of age with potential accidental paracetamol

intoxication, gastrointestinal decontamination with syrup of ipecac, activated charcoal or gastric lavage is not indicated.

In awake, cooperative adults, 50 grams(g) of activated charcoal should be administered within 2 hours of ingestion of a toxic dose of paracetamol (more than 10 g or greater than 200 mg/kg (whichever is lower). Activated charcoal administered within 2 hours of ingestion reduces the absorbed paracetamol dose and the likelihood that acetylcysteine will subsequently be required.18 An exception to this is immediaterelease

paracetamol overdose of greater than 30 g, where activated charcoal should be administered up to 4 hours post-ingestion. Similarly for modified-release paracetamol ingestions activated charcoal should be administered for up to 4 hours post-ingestion and even longer in larger overdoses.

Nevertheless, if activated charcoal cannot be administered, treatment with acetylcysteine within 8 hours guarantees survival in almost all cases. Therefore, activated charcoal alone is not a life-saving treatment that may be imposed under a duty-of-care principle.

Acute paracetamol exposure with known time of ingestion

Treatment with acetylcysteine ensures survival if administered within 8 hours of

paracetamol ingestion. Beyond 8–10 hours after ingestion, efficacy decreases with increasing delay to treatment.14 If the result of a paracetamol determination can be obtained **within 8 hours** of ingestion, acetylcysteine administration may be delayed until a serum paracetamol concentration plotted on the nomogram confirms it is indicated. This is provided treatment can still be commenced within the 8-hour window if it is required. If a paracetamol concentration will not be available until > 8 hours post ingestion, commence acetylcysteine while awaiting a paracetamol concentration.

For patients that present within 8 hours, with a known time of ingestion, risk assessment is based on the serum paracetamol concentration plotted on the nomogram. Supplementary investigations such as liver function tests or a coagulation profile do not refine the risk assessment and do not provide useful baseline data or change management in this group of patients. These tests are therefore not indicated unless risk assessment for another agent requires them. Follow-up tests are only required at the conclusion of the 20-hour acetylcysteine infusion, in cases of modified-release ingestions or very large overdoses

In patients in whom a paracetamol concentration cannot be obtained until 8 or more hours after ingestion, acetylcysteine should be commenced immediately, if the reported dose exceeds the threshold for possible toxicity or the patient shows clinical signs suggestive of paracetamol hepatotoxicity (nausea, vomiting, right upper quadrant pain or tenderness). Evaluation of serum paracetamol concentration and ALT should then be performed as soon as possible. If the serum paracetamol concentration is subsequently found to be below the nomogram line and ALT concentration is < 50 U/L, acetylcysteine may be ceased. If the paracetamol concentration is above the nomogram line or ALT > 50 U/L, acetylcysteine should be continued..

Large/massive paracetamol ingestions

The majority of patients take less than 30g of paracetamol and of those that have toxic paracetamol concentrations the majority are just above the treatment nomogram line.20,21 Patients, who take much larger overdoses may have decreased paracetamol clearance and increased risk of hepatotoxicity despite usual treatment and may benefit from changes to the standard paracetamol management.22 Patients who have ingested greater than 30g of paracetamol should be given activated charcoal up until 4 hours post ingestion if awake and co-operative.

The current acetylcysteine regimen is adequate for the majority of overdoses, but many clinical toxicologists feel that simply following the standard three bag intravenous(IV) protocol may not be adequate in large/massive paracetamol overdoses.23 Patients who have a paracetamol concentrations double the nomogram are considered at higher risk of hepatotoxicity. In some studies, 5-7% of these patients will still develop hepatotoxicity despite being treated within 8 hours with acetylcysteine.

Only a small percentage of paracetamol overdoses will have a paracetamol concentration greater than double the nomogram line. Although there are no randomised control trials investigating optimum acetylcysteine dose in largeoverdoses, it is the practice of many clinical toxicologists to adjust the dose of acetylcysteine in these patients.24 It has not yet been determined who might benefit from an increase in acetylcysteine or what the optimum dose is. One approach in those patients with a paracetamol concentration more than double the nomogram line, is to double the concentration of the 16 hour infusion of acetylcysteine from 100mg/kg (current standard acetylcysteine 3rd bag infusion) to 200mg/kg IV acetylcysteine. The Poisons Information Centre or clinical toxicologist may be consulted for the most current advice on these patients. Furthermore those patients with very high concentrations often still have elevated paracetamol concentrations or develop abnormal liver function tests (LFTs) at the completion of treatment and may require prolonged acetylcysteine treatment. They should have an ALT and paracetamol concentration checked near the completion of IV acetylcysteine (ie, 2 hours prior to completion of the acetylcysteine infusion). Acetylcysteine should be continued if they have an increasing ALT (greater than 50 U/L), or a paracetamol concentration greater than 10 mg/L (66 μmol/L). Acetylcysteine can be continued at a rate of 100 mg/kg of acetylcysteine in 1000 mLof 5% dextrose over 16 hours

Acute paracetamol exposure with unknown time of ingestion

If the time of ingestion is unknown, or the treating clinician is not confident of the history of ingestion, it is safest to treat the patient as a delayed presentation. Thus, the recommendation is to follow the > 8 hours scenario in Figure 2; that is to commence acetylcysteine. If the serum paracetamol concentration is greater than 10 mg/L (66 μmol/L) or the ALT is elevated > 50 U/L, acetylcysteine treatment should be continued. Serum ALT should be repeated at the end of the acetylcysteine infusion and then if the ALT is < 50 U/L or decreasing, acetylcysteine may be discontinued. If further history becomes available and the serum paracetamol

concentration can be accurately plotted on the nomogram, this should be done and acetylcysteine discontinued if the paracetamol concentration is below the treatment line.

Repeated supratherapeutic ingestion

There is little evidence to guide risk assessment for repeated ingestion of high doses

of paracetamol. The margin of safety has for many years been assumed to be high.However, recent data suggest that minor subclinical elevations of serum ALT may bequite common with prolonged therapy.31 Conversely, studies of "high-risk" patients who have taken supratherapeutic doses over 3–4 days have suggested significant hepatotoxicity is uncommon.32 Therefore, the threshold for the reported dose that causes toxicity has been made deliberately and conservatively low However, there is evidence that the combination of a low paracetamol concentration and an ALT less than 50 U/L at any time indicates there is no risk of subsequent hepatotoxicity.33 In most cases, this rule precludes the need for prolonged treatment in this group. Patients should have a paracetamol concentration and ALT measured if they meet the criteria for supratherapeutic ingestion.

Criteria for supratherapeutic ingestion:

- more than 10 g or 200 mg/kg (whichever is lower) in a single 24-hour p
- more than 6 g or 150 mg/kg (whichever is lower) per 24 hours for the preceeding 48 hours.

Subsequent management of hepatotoxicity and liver failure

Only a small proportion of patients develop hepatotoxicity, early symptoms include nausea, vomiting, abdominal pain and right upper quadrant tenderness. The majority of these still do not develop fulminant hepatic failure and recover fully.1,14 Patients who develop abnormal liver biochemistry require an extended duration of IV acetylcysteine. Acetylcysteine is continued at the rate of the last infusion stage (100mg/kg acetylcysteine over 16 hours or 150 mg/kg/24 hours).Most experts would continue acetylcysteine until:

- The patient is clinically improving and
- ALT is decreasing and
- INR is improving and < 2
- The paracetamol concentration is less than 10 mg/L (66 mol/L).

These patients require regular clinical review and 12-hourly blood tests, or more frequently if there is clinical deterioration. Blood investigations that indicate prognosis should be performed. These include electrolytes, urea, creatinine, liver function tests, INR, blood sugar, phosphate and venous blood gas (looking at the pH and lactate).50,51 Advice may be sought from a clinical toxicologist or local Poisons Information Centre. A markedly prolonged INR is common in patients with severe hepatotoxicity and correction is not required, unless there is evidence of bleeding.Avoid correction of INR until discussion with a Liver Transplant Unit.

Patients should be discussed with a Liver Transplant Unit if they have any of the

following:

- INR > 3.0 at 48 hours or > 4.5 at any time
- Oliguria or creatinine > 200 mol/L

- Persistent acidosis (pH < 7.3) or arterial lactate > 3 mmol/L, despite resuscitation.
- Systolic hypotension with BP < 80 mmHg
- Hypoglycaemia
- Severe thrombocytopenia
- Encephalopathy of any degree, or any alteration of consciousness (GCS< 15), not associated with sedative co-ingestions.

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