ID: JCDR/2012/3944:2342

Review Article

Pharmacology Section

Management of Paracetamol Poisoning: The Old and the New

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ABSTRACT

Paracetamol is involved in a large proportion of accidental exposures and deliberate self-poisoning cases, although subsequent hepatic failure and death are the uncommon outcomes. The optimal management of most of the patients with a paracetamol overdose still remains unclear. The following article attempts to compile a management advice with the current clinical toxicology practice, revised guidelines and recent advances.

Key Words: Acetaminophen, N acetyl cysteine

INTRODUCTION

Paracetamol (acetaminophen) is the most widely used over-the-counter analgesic agent in the world and it is the leading pharmaceutical agent in overdose which leads to hospital admissions [1].

Paracetamol is involved in a large proportion of accidental paediatric exposures and deliberate self-poisoning cases, although hepatic failure and death are the uncommon outcomes [2,3].

In UK, the proportion of the overdoses with paracetamol increased from 14.3% in 1976 to 42% in 1990, and in 1993, 47.8% of all the overdoses which were reported, involved paracetamol or paracetamol-containing drugs [4]. It has also become increasingly common in countries which include Denmark and Australia [5,6].

In India, the data on paracetamol self poisoning is uncommon and it is insufficient as compared to that of the west. A 10 year retrospective hospital based study reported 0.32% cases of acute paracetamol overdoses due to accidental exposures [7].

The existing treatment recommendations use oral and intravenous N acetyl cysteine to prevent a hepatic injury and to replenish the glutathione stores.

This review summarizes the toxicokinetics and it outlines the management of paracetamol poisoning, along with the recent advances in its treatment and prevention.

BACKGROUND

Paracetamol Kinetics

Paracetamol is rapidly absorbed from the small intestine. Its peak serum concentrations occur within 1–2 hours for the standard tablet or the capsule forms. 20% of the ingested dose undergoes first-pass metabolism in the gut wall (sulphation), while the rest undergoes hepatic biotransformation.

The mechanism of paracetamol induced hepatotoxicity can be explained in the following steps:

1. 5% of the ingested paracetmol is converted by mixed function oxidases in the hepatocytes into a reactive metabolite, N acetyl p benzoquinonimine.
2. In therapeutic doses, this reactive metabolite is conjugated with glutathione and its byproducts, mercapturic acid and cysteine are excreted in urine.
3. In cases of a paracetamol overdose, the excess amount of the reactive metabolite accumulates, while the glutathione stores diminish.
4. A hepatic toxicity ensues if the glutathione stores drop to approximately 30% of their normal amounts.
5. The accumulated reactive metabolite forms covalent bonds with the SH groups in the hepatocytes, resulting in hepatic necrosis [8].

Risk Assessment

The key factors to consider for paracetamol poisoning are:

1. The dose and concentration (early) .
2. The clinical and laboratory features which suggest liver damage (late).
3. A history which suggests an increased susceptibility to the toxicity in alcoholics and malnourishment.

The serum paracetamol levels should be checked to assess the need for *N*-acetylcysteine administration in all the patients with deliberate paracetamol self-poisoning, regardless of the stated dose. A clinical or biochemical evidence of a liver injury may not be apparent for up to 24 hours after the acute paracetamol overdose. The best surrogate marker which indicates the potential for this injury is a timed serum paracetamol level which is plotted on a nomogram.

The nomogram which is used appears to be a local decision, but these local nomograms are often derived from monograms which have been devised overseas. The Prescott nomogram was based on a cohort of patients in Edinburgh and it extends from 1320µmol/L (200mg/L) at 4 hours to 200µmol/L (30mg/L) at 15 hours. The Rumack–Matthew nomogram is based on the same data, but it has been extrapolated to 24 hours. It also uses a “treatment line” that is plotted 25% lower (1000µmol/L [150mg/L] at 4 hours) to comply with a United States Food and Drug Administration requirement, to provide a “safety buffer” for research and clinical purposes. Many guidelines have recommended an arbitrary, further lowering of the

nomogram line (ie, to 660µmol/L [100mg/L] at 4 hours) for patients with such risk factors as chronic ethanol misuse, use of enzyme-inducing drugs, prolonged fasting, and dehydration [9,10].

Lab Assessment

In patients who present within 8 hours after ingestion, the evaluation of the serum paracetamol and the alanine aminotransferase (ALT) levels should be performed as soon as possible. Other recommended investigations if the patient is brought in after 8 hours are, Prothrombin time/INR, blood urea and creatinine levels, blood glucose levels and estimation of the arterial blood gas concentration.

Management of the Paracetamol Overdose

A recovery is usually seen with supportive management with *N*-acetylcysteine which is administered in routine doses, although prolonged infusions may be required.

The role of haemodialysis has been described in many settings, but the indications for its use have not been clearly outlined.

1. Gastrointestinal decontamination

The administration of activated charcoal within 4 hours of the paracetamol ingestion reduces its further absorption and the further need for N acetyl cysteine administration. The usual dose of activated charcoal in adults is 25-50 gm in 100-200 ml of water (0.5 -1 gm/kg body weight) [11].

2. Antidotes

Since it is the relative scarcity of the SH groups that leads to the hepatotoxicity which is caused by paracetamol, the definitive therapy has been directed towards the measures which are taken to restore it. The first of such agents were cysteine and methionine, which provided encouraging results by replenishing the lost glutathione stores. The use of these agents resulted in dramatic increases in the survival of the patients, but the side effects (flushing, vomiting, etc) which were associated with these therapies led the researchers to seek alternative treatments .These gave way to trials with N-acetyl cysteine, which is now the preferred antidote of choice [12].

N-Acetylcysteine

Acetylcysteine (also known as *N*-acetylcysteine) prevents the hepatic injury, primarily by restoring hepatic glutathione. It is thought to provide cysteine for the glutathione synthesis and possibly to form an adduct directly with the toxic metabolite of acetaminophen and *N*-acetyl-*p*-benzoquinoneimine and to thus prevent its covalent bonding to the hepatic proteins [13]. In addition, in patients with acetaminophen-induced liver failure, acetylcysteine improves the haemodynamic and oxygen use, it increases the clearance of indocyanine green (a measure of the hepatic clearance), and it decreases the cerebral oedema. The exact mechanism of these effects is not clear, but it may involve scavenging of the free radicals or changes in the hepatic blood flow [14, 15]. When the risk assessment indicates that *N*-acetylcysteine is required, it is administered as a three-stage infusion, with each stage containing different doses, totaling 300mg/kg over 20–21 hours [Table/Fig-1]. If hepatic injury is suspected after the three infusion stages, *N*– acetylcysteine is continued at the rate of the last infusion stage (100mg/kg each 16 hours or 150mg/kg/24 hours), until there is a clinical and biochemical evidence of improvement.

N-acetylcysteine is packaged as an intravenous infusion in 10mL ampoules, each of which contains a 2000mg (20%) dose. The prescription of *N*-acetylcysteine requires a two-stage calculation to compute the appropriate weight-based dose and then the volume is required [16].

Calculation or transcription errors may lead to potentially fatal dosing errors. It is recommended that dosing tables which provide the required volume of 20% *N*-acetylcysteine by weight categories be used to chart the volume which is required in each infusion. This precludes the need for calculations and it decreases the potential for error. Such tables are found in the *N*-acetylcysteine product information and they have also been reproduced in the new guidelines. The calculation of the *N*-acetylcysteine doses is based on the estimated lean bodyweight to the nearest 10kg. A formula is provided to calculate the *N*-acetylcysteine volume in each infusion for patients who weigh more than 90kg. For children, the dose of *N*-acetylcysteine is calculated in the same way, but with the volume being reduced appropriately. Intravenous administration of the oral N-acetylcysteine preparation appears to have limited adverse effects and this offers another mechanism of delivery of the potentially lifesaving N-acetylcysteine when an oral administration is not possible.

Only a small proportion of the patients who present late develop severe hepatotoxicity and fulminant hepatic failure. The clinicians should consult a specialist from the liver unit for advice on the management of patients with liver failure or with signs that indicate a poor prognosis [17].

Adverse Effects

The most commonly reported adverse effects of intravenous acetylcysteine are anaphylactoid reactions, including rash, pruritus, angio-oedema, bronchospasm, tachycardia, and hypotension. The most severe adverse effects occur with the erroneous dosing of intravenous acetylcysteine in children. These effects includes cerebral oedema and hyponatraemia (due to its administration in 5% dextrose). There are rare reports of deaths which were caused due to anaphylactoid reactions [18,19,20].

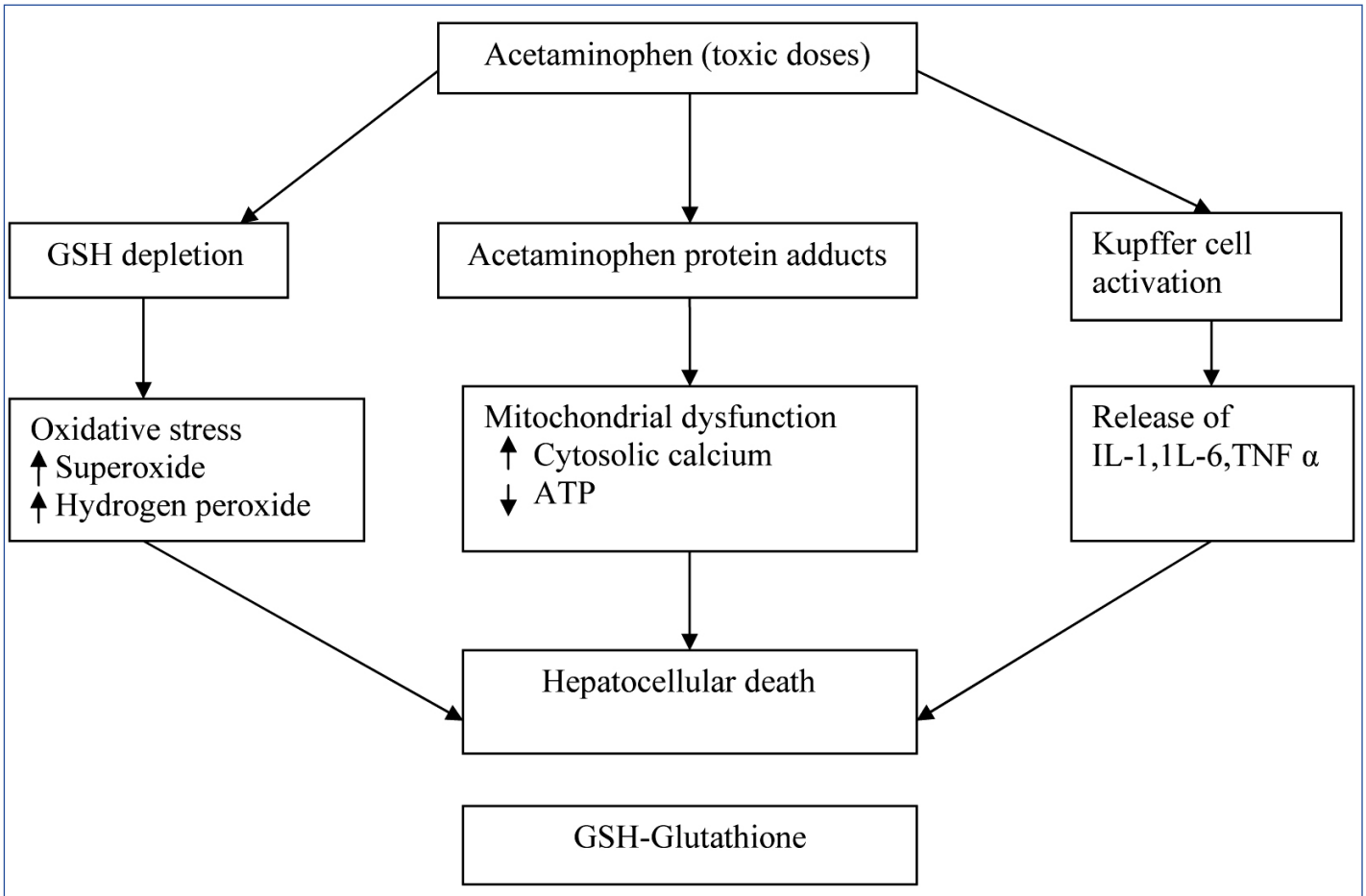
Recent Advances

The pathophysiology of hepatic necrosis following an overdose of acetaminophen has been studied extensively. The following are the hypothesized molecular mechanisms that have been put forth, as has been depicted in [Table/Fig-2].

1. Oxidative stress
2. Kupfer cell activation
3. Nitration of the acetaminophen adducts with peroxynitrate formation
4. NOS

A. Initial infusion
An initial dose of 150mg/kg of *N*-acetylcysteine diluted in 200mL of 5% glucose and infused over 15 to 60 minutes.
B. Second infusion
Initial infusion is followed by a continuous infusion of 50mg/kg of *N*-acetylcysteine in 500 mL of 5% glucose over the next 4 hours.
C. Third infusion
Second infusion is followed by a continuous infusion of 100mg/kg of *N*-acetylcysteine in 1000 mL of 5% glucose over the next 16 hours.

[Table/Fig-1]: Three-stage *N*-acetylcysteine infusion



[Table/Fig-2]: Hypothesis of acetaminophen induced hepatocellular injury

5. IL-1β and other cytokines such as IL-10, macrophage inhibitory protein-2 (MIP-2), and monocyte chemoattractant protein-1 (MCP-1), appear to be involved in hepatocyte repair and in the regulation of proinflammatory cytokines [21].

Many animal models have used agents that will reverse the oxidative stress mediated hepatic damage which is caused by acetaminophen. Allopurinol, which attenuated acetaminophen protein-adduct formation, mitochondrial dysfunction and oxidant stress, eliminated the hepatocellular nitrotyrosine staining and injury [22].

The protective effect of deferoxamine against the APAP-induced liver injury may be attributable to the chelation of iron, which can catalyze the generation of active oxygen species in hepatocytes H. Najafzadeh et al., observed that vanadium had a better effect than deferoxamine in the prevention of the hepatotoxicity which was induced by APAP, although the mechanism of its effect was unclear [23].

CONCLUSION

The antidote, N- acetylcysteine should be given to all the patients with a serum paracetamol concentration of >200 mg/l. The treatment with *N*-acetylcysteine guarantees a survival if it is administered within 8 hours of the paracetamol ingestion, and the outcome is the same, regardless of when the treatment is given within this 8-hour window. If the antidote is not given, over 60% of the patients with serum paracetamol concentrations above the treatment line may develop serious liver damage, and of these, about 5% will die. Beyond 8–10 hours after the ingestion, the efficacy decreases with an increasing delay in the treatment. The optimal route and the duration of the administration for N-acetylcysteine in the management of the acetaminophen (paracetamol) poisoning are controversial. Recent studies have stated that a shorter hospital stay, patient and doctor convenience, and the concerns over the reduction in the bioavailability of oral N-acetylcysteine by charcoal and vomiting make intravenous N-acetylcysteine preferable for most of the patients with acetaminophen poisoning.

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FINANCIAL OR OTHER COMPETING INTERESTS:
None.

Date of Submission: **Nov 5, 2011**
Date of Peer Review: **Dec 31, 2011**
Date of Acceptance: **Jun 29, 2012**
Date of Publishing: **Aug 10, 2012**