Paracetamol Toxicity- An Overview

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Introduction

Paracetamol (acetaminophen) is a safe, effective, well-tolerated and cheap analgesic and anti-pyretic drug with relatively few adverse effects when used at the recommended therapeutic dosage. It was first introduced in the year 1955 for its clinical application and since then, it is widely used almost throughout the world. In many countries the drug is readily available over-the-counter without the need of prescription. It’s easy availability and no need for prescription made it one of the commonest drugs used for suicidal or self harm purposes. Its toxicity was noticed in the 1960s [1]. Since then number of cases coming to the emergency department kept on increasing, especially in UK [2,3]. It is also a frequent cause of poisoning in many other countries, including North America, Australia and New Zealand and several other countries in Europe [4-9]. Increasing number of the cases brought the idea of legalization of drug from over the counter policy to prescription only status. Following legislation in 1998 to limit pack sizes, beneficial effects on paracetamol-related mortality and morbidity were reported in England. Although following legislations to limit pack sizes, morbidity and mortality reduced, however strict measures are required to reduce breaches of sales guidelines [10,11]. Role of media and internet should be more emphasized in awareness about hepatic failure due to paracetamol toxicity.

With this background we review the clinical features, pharmacology, management and preventive measures to reduce the load to intentional toxicity.

Epidemiology

Paracetamol is easily available in market, and lay people commonly underestimate its toxicity. Paracetamol toxicity is one of the most common causes of poisoning worldwide [12]. Currently paracetamol is the most common cause of ALF in both United States and United Kingdom, with a trend to increasing incidence in the United States [13]. A national network was established to track cases of acute liver failure in the United States, found that nearly half the cases were attributable to paracetamol, and intentional (suicidal) and unintentional (chronic) poisonings accounted equally for the cases of paracetamol- associated hepatic failure [14]. Pediatric paracetamol exposures account for approximately 30,000 reports to the National Poison Data System annually in United States [15]. In Oxford, UK, the proportion of overdoses with paracetamol increased from 14.3% in 1976 to 42% in 1990, and in 1993, 47.8% of all overdoses involved paracetamol or paracetamol- containing drugs [16]. It has also become increasingly common in countries like Denmark and Australia [17,18]. In Scotland, the rate of paracetamol overdose increased almost 400% between 1981–83 and 1991–93 [19].

Pharmacology

Paracetamol has excellent anti-pyretic activity, moderate analgesic and almost no anti-inflammatory property. It acts by inhibiting prostaglandin synthesis by its action on cyclo-oxygenase-3 enzyme, (an alternate splice product of cox-1 enzyme) [20].

The therapeutic dose of paracetamol is 0.5-1 g in adult (maximum of 4 g/day) and 10-15 mg/kg every 4-6 hours in children [21]. It is indicated for the symptomatic relief of fever, mild musculoskeletal pain, headache, migraine. The most common route of administration is the oral route (in the form of tablets, effervescent tablets & suspension); other routes are the rectal route as suppository and in hospital settings, it can be given via intravenous infusion.

Following an oral dose, the drug is well absorbed from the gastrointestinal tract, reaching a peak plasma concentration within 30-60 minutes. The drug is metabolized in the liver, 80% of an administered dose (therapeutic dose), undergoes glucuronide conjugation and sulphate conjugation; the remaining drug undergoes hydroxylation to form a highly reactive oxidative product, N-Acetyl P Benzo-quineime (NAPQI), which in turn conjugates with glutathione, GSH to form mercapturic acid and is eliminated in urine [22].

Hepato toxicity generally occurs when the glutathione stores fall to less than 30% of the normal [23]. The supply of hepatic GSH is limited and in case of overdose of paracetamol, the amount of NAPQI formed is greater than the GSH available such that NAPQI is not conjugated and being an active product, it exerts hepato-toxic effects and also causes renal tubular necrosis by reacting with the nuleophilic aspects of the cells. Paracetamol in the dose of 10-15 g can potentially lead to fatal hepato- toxicity [24]. Severe hepato cellular damage and renal tubular necrosis can result from taking 150 mg/kg (about 5-10 g) in a single dose [25].

The risk of hepato cellular injury is increased by any condition that leads to an increase in the production of NAPQI (patients on some drugs like Rifampicin, Phenobarbionate, Phenytioin, Carbamazepine, etc.) or conditions with low GSH reserves such as fasting, malnutrition, alcoholic related or other types of liver diseases, HIV positive patients, cystic fibrosis and genetic variation.

Effects on Internal Organs

Pathologic evaluation of various organs shows that the liver is a primary target for toxicity after paracetamol overdose because the hepatocytes elaborate NAPQI. As NAPQI has a short life span, it can damage only cells that elaborate it. Overdose of paracetamol may produce severe liver injury with hepato cellular necrosis. The important mechanisms of cell injury are metabolic activation of paracetamol, glutathione depletion, alkylation of proteins, especially mitochondrial proteins, and formation of reactive oxygen/nitrogen species [25].

Grossly liver is usually of normal size with mottled external surface. On light microscopy liver shows large areas of coagulative...
necrosis; with some typical geographic or zonal pattern, necrosis is typically perivascular/centrilobular/acinar Zone 3 i.e. around central vein, however it spares periportal areas (around portal triad) [25,26]. This zonal distribution is characteristically a feature of liver injury associated with paracetamol overdose and can well be explained by the fact that periportal areas have more drug metabolizing enzymes than elsewhere; so more toxic metabolites are formed in these cells making them susceptible to injury. Sparse inflammatory infiltrate by lymphocytes and macrophages is also seen.

Various studies in human and animal models have shown that paracetamol overdose may lead to renal dysfunction [27-30]. Overall, renal insufficiency occurs in approximately 1-2% of patients with paracetamol overdose [31]. Effects on the kidney are seen more in children and adolescents as compare to adults. The mechanism of paracetamol toxicity is not well understood in the kidney. Possible mechanisms, based on human and animal data, show the role of cytochrome P-450 pathway, as well as prostaglandin synthetase, and Ndeacetylase enzymes [27]. The renal damage is usually in form of acute tubular necrosis both clinically and histologically. Light microscopy shows normal glomeruli and vessels with tubular epithelial cell necrosis [32]. Tubular swelling with loss of the tubular brush border and distortion of mitochondrial organization are often seen on electron microscopy [33].

Clinical Presentation

The clinical signs usually do not become apparent for the first 24-48 hours after an acute overdose of paracetamol [20]. Liver failure may occur between 2-7 days following the ingestion. The clinical course of paracetamol toxicity is generally divided into 4 phases [34].

Phase 1 (0-24 hrs)

The patient is usually asymptomatic or may present with features like anorexia, nausea, vomiting and malaise. The liver Function Tests, shows a mild increase in the serum transaminase level (begins to rise approximately 12 hours after an acute ingestion).

Phase 2 (18-72 hrs)

The patient usually experience nausea, vomiting, abdominal pain (right upper quadrant). On examination, tenderness is present on the right upper quadrant; tachycardia and hypotension are usually present. Serum transaminase level continues to rise.

Phase 3 (72-96 hrs) Hapatic phase

This is the most critical phase. The patient is severely ill. Jaundice, coagulopathy with bleeding tendencies, hypoglycemia, hepatic flail and hepatic encephalopathy occur as a result of hepatic necrosis and dysfunction. Metabolic acidosis with acute renal failure (due to hepato renal syndrome) may develop. Death usually occurs as a consequence of multi-organ failure.

Phase 4 (4 days-3 weeks) Recovery phase

Patients who survive the critical illness of phase 3, are more likely to improve with with resolution of the symptoms and organ failure.

Investigation

The investigations include the timed serum paracetamol concentration, liver function tests (including prothrombin time or international normalised ratio) and kidney function tests. These tests are needed to assess risk and monitor progress. The plasma concentration of paracetamol has predictive value, if it lies above a semi-logarithmic graph which is obtained by joining the points between 1.32 mmol/L at 4 hours after ingestion to 0.33 mmol/L at 12 hours, then prognosis is poor and serious hepatic damage is likely to occur [35].

Treatment

The aim of the management of paracetamol toxicity focuses on the prevention of hepatotoxicity by appropriate line of treatment which is achieved by limiting the absorption of the drug and by decreasing the toxic impact of NAPQI through replenishment of glutathione store.

The general principle for limiting the drug absorption applies only if the patient is seen within the first hour of acute ingestion of paracetamol. Gastric lavage with small amounts of tap water at ambient temperature followed by drinking of the activated charcoal solution immediately after the removal of tube decreases the absorption of paracetamol by 50-90%. The combination treatment comprising gastric lavage followed by activated charcoal may be replaced by charcoal alone, even in patients presenting with larger overdoses who arrive within 1 h of drug ingestion [36].

Specific treatment is carried out with N-Acetyl Cysteine (NAC). The treatment of paracetamol toxicity with NAC is originated in UK in the year 1970. The World Health Organization Model List of Essential Medicines and Model Formulary of 2006 lists Acetyl Cysteine (NAC) as an antidote for use in the treatment of paracetamol overdose [37]. NAC is best given within the first 8 hours following an acute overdose for maximum hepatoprotective effects. A study published in 1988 found that NAC is uniformly effective if given within eight hours of a single overdose, but subsequently its efficacy falls [38]. A controlled trial provided evidence that NAC can improve outcome even in patients with encephalopathy, so those who present more than eight hours after overdose are still treated with this antidote [39].

The Medicines and Healthcare products Regulatory Agency (MHRA) has simplified the guidelines on the management of paracetamol overdose in 2012. All patients who have a timed plasma paracetamol level plotted on or above the line drawn between 100 mg/L at 4 hours and 15 mg/L at 15 hours after ingestion should receive NAC regardless of any risk factors they may have for hepato toxicity [40]. The treatment is continued until the patient is clinically stable and the liver transaminase level has fallen to less than 1000 IU/L along with normalization of the clotting screen or till the patient receives a liver transplantation [40].

NAC can be administered by oral and intravenous route. The intravenous route is preferred in the presence of fulminant hepatic failure or if there is intolerance to oral therapy such as the patient is vomiting. Otherwise, the oral route of administration remains the stay of treatment. NAC oral dosing schedule is as loading dose of 140 mg/kg followed by 70 mg/kg every 4 hours, to be continued for 72 hours. If vomiting occurs within 1 hour of ingestion of the drug, the dose has to be repeated. NAC intravenous dosage schedule is a total dose of 300 mg/kg approximately over a period of 20 hours is given in a phasic regimen via intravenous infusion as 150 mg/kg in 200 ml of 5% glucose over 15 minutes, 50 mg/kg in 500 ml of 5% glucose over 4 hours and 100 mg/kg in 1000 ml of 5% glucose over 16 hours [41].

Intravenous NAC is associated with higher incidence of adverse effects such as rashes, pruritus (decreased by giving anti-histaminic like Chlorpheniramine), nausea, vomiting, hyponatremia and anaphylactoid reaction [42]. The anaphylactoid reaction is mediated by histamine and depends on the blood level of NAC. In the event of development of an anaphylactoid reaction, the NAC therapy has to be discontinued and treatment with adrenaline, corticosteroid and anti-
histaminic has to be started immediately along with other supportive measures [35].

Other modalities of treatment of paracetamol toxicity includes fluid replacement, symptomatic treatment of vomiting with drugs like metoclopramide, vitamin K injection- 10 mg intravenously for bleeding diathesis, correction of acidosis with sodium bicarbonate and liver transplantation in cases of fulminant hepatic failure.

References