ISSN: 2165-7548

Mini Review **Open Access**

Paracetamol Toxicity- An Overview

Tasneem Ibrahim[1]*, Smriti Agnihotri[2] and Arun Kumar Agnihotri[3]

[1] Lecturer, Department of Pharmacology, SSR Medical College, Mauritius
[2] Professor, Department of Pathology, SSR Medical College, Mauritius
[3] Department of Forensic Medicine & Toxicology, SSR Medical College, Mauritius

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 gastro-intestinal 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 glucoronide 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 nucleophilic 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, Phenobarbitone, Phenytoin, 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 perivenular/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 perivenular 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 flap 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 invesitgations 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 hepato- protective 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 metopimazine, vitamin K injection- 10 mg intravenously for bleeding diasthesis, correction of acidosis with sodium bicarbonate and liver transplantation in cases of fulminant hepatic failure.

References

1. Sheen CL, Dillon JF, Bateman DN, Simpson KJ, Macdonald TM (2002) Paracetamol toxicity: epidemiology, prevention and costs to the health-care system. QJM 95: 609-619.

2. Prescott K, Stratton R, Freyer A, Hall I, Le Jeune I (2009) Detailed analyses of self-poisoning episodes presenting to a large regional teaching hospital in the UK. Br J Clin Pharmacol 68: 260-268.

3. Bergen H, Hawton K, Waters K, Cooper J, Kapur N (2010) Epidemiology and trends in non-fatal self-harm in three centres in England: 2000-2007. Br J Psychiatry 197: 493-498.

4. Larson AM, Polson J, Fontana RJ, Davern TJ, Lalani E, et al. (2005) Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. Hepatology 42: 1364-1372.

5. Nourjah P, Ahmad SR, Karwoski C, Willy M (2006) Estimates of acetaminophen (Paracetomal)-associated overdoses in the United States. Pharmacoepidemiol Drug Saf 15: 398-405.

6. Daly FF, Fountain JS, Murray L, Graudins A, Buckley NA; Panel of Australian and New Zealand clinical toxicologists (2008) Guidelines for the management of paracetamol poisoning in Australia and New Zealand--explanation and elaboration. A consensus statement from clinical toxicologists consulting to the Australasian poisons information centres. Med J Aust 188: 296-301.

7. Wei G, Bergquist A, Broomé U, Lindgren S, Wallerstedt S, et al. (2007) Acute liver failure in Sweden: etiology and outcome. J Intern Med 262: 393-401.

8. Canbay A, Jochum C, Bechmann LP, Festag S, Gieseler RK, et al. (2009) Acute liver failure in a metropolitan area in Germany: a retrospective study (2002 - 2008). Z Gastroenterol 47: 807-813.

9. National Suicide Research Foundation (2009) National Registry of Deliberate Self-Harm.

10. (1997) The Medicines (Sales or Supply) (Miscellaneous Provisions) Amendment (No 2) Regulations 1997. London, The Stationery Office.

11. Hawton K, Townsend E, Deeks J, Appleby L, Gunnell D, et al. (2001) Effects of legislation restricting pack sizes of paracetamol and salicylate on self poisoning in the United Kingdom: before and after study. BMJ 322: 1203-1207.

12. Gunnell D, Murray V, Hawton K (2000) Use of paracetamol (acetaminophen) for suicide and nonfatal poisoning: worldwide patterns of use and misuse. Suicide Life Threat Behav 30: 313-326.

13. Chun LJ, Tong MJ, Busuttil RW, Hiatt JR (2009) Acetaminophen hepatotoxicity and acute liver failure. J Clin Gastroenterol 43: 342-349.

14. Lee WM (2004) Acetaminophen and the U.S. Acute Liver Failure Study Group: lowering the risks of hepatic failure. Hepatology 40: 6-9.

15. Bronstein AC, Spyker DA, Cantilena LR Jr, Green JL, Rumack BH, et al. (2011) 2010 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 28th Annual Report. Clin Toxicol (Phila) 49: 910-941.

16. Hawton K, Ware C, Mistry H, Hewitt J, Kingsbury S, et al. (1996) Paracetamol self-poisoning. Characteristics, prevention and harm reduction. Br J Psychiatry 168: 43-48.

17. Ott P, Dalhoff K, Hansen PB, Loft S, Poulsen HE (1990) Consumption, overdose and death from analgesics during a period of over-the-counter availability of paracetamol in Denmark. J Intern Med 227: 423-428.

18. Gow PJ, Smallwood RA, Angus PW (1999) Paracetamol overdose in a liver transplantation centre: an 8-year experience. J Gastroenterol Hepatol 14: 817-821.

19. McLoone P, Crombie IK (1996) Hospitalisation for deliberate self-poisoning in Scotland from 1981 to 1993: trends in rates and types of drugs used. Br J Psychiatry 169: 81-85.

20. Rang HP, Dale MM, Ritter JM, Flower RJ (2008) Pharmacology. (6th edn), Churchill Livingstone, UK.

21. Royal Pharmaceutical Society (2003) British National Formulary. BNF publication, London.

22. Grahame-Smith DG, Aronson JK (2002) Oxford textbook of clinical Pharmacology and drug Therapy. (3rd edn), Oxford University Press, New York.

23. Mitchelle JR, Jollow DJ, Potter WZ, Davis DC, Gillette JR, et al. (1973) Acetaminophen-induced hepatic necrosis-I Role of drug metabolism. J Pharmacol Exp Ther 187: 185-194.

24. Benette PN, Brown MJ (2009) Clinical Pharmacology. (10th edn) Churchill Livingstone, UK.

25. Radosavljević T, Mladenović D, Vucević D, Vukićević RJ (2010) [The role of oxidative/nitrosative stress in pathogenesis of paracetamol-induced toxic hepatitis]. Med Pregl 63: 827-832.

26. James LP, Mayeux PR, Hinson JA (2003) Acetaminophen-induced hepatotoxicity. Drug Metab Dispos 31: 1499-1506.

27. Cobden I, Record CO, Ward MK, Kerr DN (1982) Paracetamol-induced acute renal failure in the absence of fulminant liver damage. Br Med J (Clin Res Ed) 284: 21-22.

28. Curry RW Jr, Robinson JD, Sughrue MJ (1982) Acute renal failure after acetaminophen ingestion. JAMA 247: 1012-1014.

29. Kleinman JG, Breitenfield RV, Roth DA (1980) Acute renal failure associated with acetaminophen ingestion: report of a case and review of the literature. Clin Nephrol 14: 201-205.

30. Cockcroft DW, Gault MH (1976) Prediction of creatinine clearance from serum creatinine. Nephron 16: 31-41.

31. Prescott LF (1983) Paracetamol overdosage. Pharmacological considerations and clinical management. Drugs 25: 290-314.

32. Björck S, Svalander CT, Aurell M (1988) Acute renal failure after analgesic drugs including paracetamol (acetaminophen). Nephron 49: 45-53.

33. Bessems JG, Vermeulen NP (2001) Paracetamol (acetaminophen)-induced toxicity: molecular and biochemical mechanisms, analogues and protective approaches. Crit Rev Toxicol 31: 55-138.

34. Farrell SE (2013) Acetaminophen Toxicity.

35. Ferner RE, Dear JW, Bateman DN (2011) Management of paracetamol poisoning. BMJ 342: d2218.

36. 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: 312-317.

37. WHO Model List of Essential Medicines (2007) World Health Organization.

38. Smilkstein MJ, Knapp GL, Kulig KW, Rumack BH (1988) Efficacy of oral N-acetylcysteine in the treatment of acetaminophen overdose. Analysis of the national multicenter study (1976 to 1985) N Engl J Med 319: 1557-1562.

39. Keays R, Harrison PM, Wendon JA, Forbes A, Gove C, et al. (1991) Intravenous acetylcysteine in paracetamol induced fulminant hepatic failure: a prospective controlled trial. BMJ 303: 1026-1029.

40. Paracetamol overdose: new guidance on treatment with intravenous N-acetyl Cysteine (2012) Drug Safety Update 6: S2.

41. Royal Pharmaceutical Society (2013) British National Formulary. London: BNF publication.

42. Whyte IM, Francis B, Dawson AH (2007) Safety and efficacy of intravenous N-acetylcysteine for acetaminophen overdose: analysis of the Hunter Area Toxicology Service (HATS) database. Curr Med Res Opin 23: 2359-2368.