



A Critical Review On Paracetamol Induced Hepato-Toxicity

Dr. Jaiprakash surajalal ukey

Associate professor

Department of Agadtantra

M.S.Ayurvedic Medical College Hospital and Research Institute Kudwa, Gondia

ABSTRACT

Paracetamol, also known as acetaminophen, is the most commonly used antipyretic and pain reliever. Over the counter availability and a good safety profile make paracetamol one of the most common analgesic in developed countries but also the leading cause of liver failure due to overdose. Paracetamol toxicity is one of the most common causes of poisoning world wide. While paracetamol is described as relatively nontoxic when administered in therapeutic doses, it is known to cause toxicity when taken in a single or repeated high dose, or after chronic ingestion. We herein review the literature on paracetamol toxicity with particular attention to aspects of liver damage and related fatalities.

KEYWORDS: Paracetamol, Hepatotoxicity, drug overdose, Liver toxicity

INTRODUCTION

Paracetamol also known as acetaminophen is the most commonly used antipyretic and pain reliever and since 1955 has been available over the counter as a single formulation or in combination with other substances^[1]. It is a drug of choice in patients, in whom administration of non-steroidal and anti-inflammatory drugs is contraindicated, such as in case of gastric ulcers, hypersensitivity to aspirin, impairments in blood coagulation, in pregnant women, nursing mothers and children with elevated body temperature associated to a disease^[2].

Although many side effects following drug use had been registered since the approved use in the 50s, its hepatotoxicity was not significantly recognized until 1980. Cases of fatal drug-related hepatotoxicity dubbed “therapeutic misadventures” and the association of paracetamol poisoning with alcohol were firstly reported during the mid 1980s^[3].

While paracetamol is described as relatively nontoxic when administered in therapeutic doses^[4], it is known to cause toxicity when taken in a single or repeated high dose, or after chronic ingestion.

Moreover, there are several factors that may contribute to an increased risk of hepatotoxicity related to the administration of paracetamol at therapeutic dose i.e. alcohol abuse, malnutrition, underlying or pre-existing liver disorders and concomitant ingestion of other potentially hepatotoxic drugs ^[5]

MATERIAL AND METHODS

Incidence of hepatotoxicity

Paracetamol overdose is among one of the commonest cause of acute liver failure in some countries. The common settings for paracetamol induced liver injury are suicidal overdose, unintentionally or accidentally in alcoholics and with therapeutic use^[6]. Studies done in adult population have shown the most common etiology of acute liver failure (40%) was paracetamol overdose, more with unintentional intake rather than taken for suicide ^[7,8]. However a multicenter prospective study of pediatric patients reported that only 14% of acute liver failure is attributed to paracetamol overdose^[9]. Due to delayed presentation and treatment, risk of mortality is comparatively more with unintentional overdosage^[10]. In chronic alcoholics, paracetamol-induced hepatotoxicity has been well recognized and reported to occur at lower doses compared with non-alcoholics^[11,12]. Paracetamol hepatotoxicity had been found with ingestion of therapeutic doses in individuals with malnutrition, advance age, chronic pulmonary diseases, cardiac dysfunction, and chronic liver disease ^[13]. Drug interactions of paracetamol with other drugs (eg. Anticonvulsants, antitubercular) also result in hepatotoxicity at lower doses ^[14,15].

HEPATOTOXICITY OF PARACETAMOL

After the administration of an oral dose, paracetamol is rapidly absorbed by the intestine, because of its weak acidity and lipi-solubility. Then, an amount between 50 and 60% is converted to its main and pharmacologically inactive glucuronidated and sulfated conjugates eliminated in urine.

In liver microsomes, a small percentage of paracetamol (5-10%) is converted by cytochrome P450 isoforms into a reactive metabolite, N-acetyl-para-benzo-quinone imine, that is primarily related to paracetamol hepatotoxicity^[16]. About 2% of paracetamol is excreted in urine unchanged ^[17].

TOXIC DOSE IN ADULTS AND CHILDREN

In single oral ingestion, the toxic dose for children is more than 200 mg/kg of body weight, whereas in adults and adolescents, it is more than 7.5g. In children younger than 6 years of age, toxicity occurs after ingestion of more than 75 mg/kg body weight per day. Acute toxic dose is in a single dose in repeated dosing ^[18]. Children are found to be less sensitive to acute intoxication than adults, and this may be due to larger glutathione stores and comparatively larger liver ^[19].

PATHOPHYSIOLOGY

Paracetamol enters the enterohepatic circulation after absorption in the gut and the liver by glucuronidation and sulfation 95% of its metabolized, and only a small amount of the drug is removed by the kidneys. In therapeutic doses, 2.7 hours is the mean elimination half-life of paracetamol ingestion ^[20]. Studies conducted in the mouse model of paracetamol overdose showed paracetamol adduct formation occurs in centrilobular hepatocytes^[21]. Liver biopsy if done, the histopathology of the liver tissue shows centrilobular hemorrhagic necrosis with no or little inflammatory reaction and normal histologic appearance of portal tracts ^[22].

CLINICAL MANIFESTATION AND LABORATORY FINDINGS

The most common symptoms are malaise, nausea with/without vomiting and abdominal pain, as these symptoms are not peculiar leading to difficulty in making the diagnosis in absence of a history of overdose. The clinical course of paracetamol hepatotoxicity has four established sequential phases^[23]. Each phase usually occurs following a fixed time interval after the paracetamol over-ingestion. The first phase starts within the first 24 hours of intake of the drug and usually has symptoms such as nausea, vomiting, muscle aches, dullness, and perspiration. However, some patients may remain asymptomatic in this phase, which leads to a delay in the diagnosis in patients who are unaware of their overdose. In the second phase that occurs 24 hrs to 72 hrs after intake, transaminases and bilirubin begins to rise and prothrombin time may be prolonged ^[24,25]. In phase 3 that occurs 72 hrs to 96hrs after ingestion, liver injury occurs maximally in this phase and is characterized by continued progression of hepatotoxicity, possibly fulminant hepatic failure and the onset of multiorgan system failure and hypoglycemia, jaundice, oliguria, acute tubular necrosis, encephalopathy, CNS systems including confusion, somnolence or coma. The risk of mortality is maximum in the 3rd phase, mostly due to multi-organ dysfunction. Phase 4 occurs after approximately 96 hrs after recovery from the 3rd phase the patient may either die from liver failure and its complication or start to recover. Those who improve liver functions usually return to normal within three weeks with the histological improvement of the liver within 3 months. Usually, the 4th phase lasts for 1 to 2 wks, but its duration varies from patient to patient. Usually bilirubin levels do not go higher as compared with liver failure due to other etiology^[26].

FACTORS influencing APAP-related hepatotoxicity

The most essential determining factor in both the development and severity of APAP hepatotoxicity is the drugs ingested dose, but some argue that the length of time from APPAP ingestion to N-acetylcysteine therapy is equally if not more important^[27,28,29]. Liver metabolism during glucouronidation or sulfation, CYP activity and maintenance of hepatic GSH supply depends on patient factors such as age, nutritional status, pre-existing liver disease, concurrent use of alcohol and other liver metabolism medication, genetic predispositions and most importantly, the acuity or chronicity of APAP overuse^[30]

ALCOHOL

The co-ingestion of alcohol and APAP is expected to cause acute hepatotoxicity. As it turns out, the manner in which alcohol is consumed plays a significant role in who may or may not suffer APAP-related hepatotoxicity^[31,32]

Phosphate in APAP hepatotoxicity

Phosphate has historically been associated with poor outcomes in patient with APAP hepatotoxicity, with early studies showing an association between low phosphate levels and increased morbidity and mortality^[33]

Age and genetic factors

APAP, an analgesic utilized by patients from infancy into the geriatric years, shows age-related hepatotoxic tendencies. In general, younger patients are betterable to overcome acute liver failure as a result of APAP hepatotoxicity, probably due to the larger hepatic cell mass that is present in this population before the cell damage occurs as well as the better capacity of those cells for non-toxic metabolism and their improved capacity for regeneration. 20 Patients over 40 yrs old who overdose on APAP portened a higher risk of acute liver failure, liver transplantation and death. In general, APAP metabolism appears age-dependant, with elderly patients being at higher risk of hepatotoxicity after acute overdose of APAP than the pediatric population^[34]

Chronic liver disease

APAP metabolism is reduced in patients with cirrhotic livers, as compared to those with normal livers. Chronic liver disease patients who use alcohol infrequently do not appear to be an elevated risk of developing APAP hepatotoxicity^[35,36,37]. Although ideally a different choice of anti-pyretic or analgesic may be used, a less than 4000 mg per use of APAP in the cirrhotic patient may be safe in the short term. More conservative dose limits, such as 2000 mg per day, have been recommended, especially for patients in whom the liver disease is marked with hepatic decompensation or active alcohol abuse.

Pregnancy

APAP is considered the most frequently prescribed analgesic in pregnancy^[38]. Pregnancy is a high risk state for many medication and APAP is no exception. Unfortunately, APAP toxicity in pregnancy can result in significant morbidity and mortality for both the mother and the fetus. APAP can freely cross the selective maternal-fetal barrier of the placenta, after which it can then be metabolized by fetal hepatocytes, causing fetal hepatic necrosis if appropriate therapy with NAC is not administered in a timely manner^[39].

Other Side Effects of Paracetamol

Paracetamol induced liver necrosis has been studied extensively , but the extrahepatic manifestation of paracetamol toxicity are currently not well described in the literature. Renal insufficiency occurs in approximately 1-2 % paracetamol users following overdose¹⁸. Limited data in a retrospective case series of pediatric patients with paracetamol poisoning suggests that associated nephrotoxicity may be more common in children and adolescents ^[40]. Although the data are limited, it is reasonable to assume that patients with anephrotoxicity risk may be similar to those at risk for hepatotoxicity i.e. patients with depleted glutathione due to starvation, fasting or alcoholism.

Some studies suggest that paracetamol has an adverse cardiovascular safety profile ⁴³ and because this substance has been shown to inhibit COX-2, it has the potential to increase blood pressure and promote thrombosis.

CONCLUSION

Paracetamol ingestion and subsequent hepatotoxicity is a critical problem that continues to plague individuals across the world. Due to its low cost and easy access, paracetamol is an ubiquitous analgesic and anti-pyretic drug available off the counter and in prescription only medication formulations. The morbidity and mortality from paracetamol overdose vary from patient to patient and also depend on underlying comorbidities , nutritional status, history of alcoholism and coingestion of other drugs. Overdose may result in mild liver injury, clinically significant hepatotoxicity or death and timely administration of antidote directs prognosis. Death from paracetamol overdose in developed countries has decreased to 1-2% after the use of N-Acetyl cysteine, which was previously much higher (6-25%)

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