

Hepatotoxicity of paracetamol and related fatalities

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Abstract. – Paracetamol, also known as acetaminophen, is the most commonly used antipyretic and pain reliever and since 1955 it is available over-the-counter as a single formulation or in combination with other substances and, as indicated by the World Health Organization, it can be used in all the three steps of pain intensity. Paracetamol toxicity is one of the most common causes of poisoning worldwide. 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. Repeated supra-therapeutic misuse, non-intentional misuse, and intentional ingestion may all result in hepatic toxicity, the main cause of acute liver failure (ALF) in the United States and Europe. Since paracetamol is responsible for nearly half of the cases in the US of acute liver failure and remains the leading cause of liver transplantation, continued awareness promotion, education and research should be constantly undertaken.

We herein review the literature on paracetamol toxicity with particular attention to aspects of liver damage and related fatalities.

Key Words:

Paracetamol, Hepatotoxicity, Fatalities, Liver toxicity.

Introduction

Paracetamol, also known as acetaminophen (IUPAC name: N-(4-hydroxyphenyl)ethanamide), 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 substances¹.

As indicated by the World Health Organization this drug can be used in all the three steps of pain

intensity. Being the main drug prescribed for febrile pains, it can be used together with non-steroidal analgesic drugs also to treat pains of moderate intensity. When pain persists or increases, paracetamol is used as an additional analgesic in combination with weak (e.g. tramadol) or strong (e.g., morphine, fentanyl) opioids. Moreover, it is a drug of choice in patients, in whom administration of non-steroidal anti-inflammatory drugs is contraindicated, such as in the 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 (fever related to illness)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 1980s³.

While paracetamol is described as relatively nontoxic when administered in therapeutic doses⁴, it is known to cause toxicity when taken in a single or repeated high dose, or after chronic ingestion.

The usual dosing of immediate-release oral preparations in adults is 325-650 mg every 4-6 hours or 1 g every 4-6 hours as necessary, without exceeding 4 g per day⁵. Conversely, in children, the recommended dose is 10-15 mg/kg every 4-6 hours up to a maximum daily dose of 50-75 mg/kg⁶. Adverse events typically associated with paracetamol intoxication are represented by acute liver failure (ALF), centrilobular hepatic necrosis, renal tubular necrosis and hypoglycaemic coma^{6,7}.

According to recent information provided by the American National Poison Data System (NPDS), paracetamol is one of the 25 drugs associated with the largest number of fatalities, either alone or in combination with other medications⁸. Paracetamol overdoses are the leading cause of acute poisoning in the United States and represent about 39%^{9,10} of all cases of acute hepatic injury. Furthermore, paracetamol is still the almost exclusive cause of liver transplantation related to an acute drug overdose, with an average of one case per six million inhabitants per year in European countries such as France, Greece, Ireland, Italy, the Netherlands, Portugal and the UK¹¹. This seems to be about eight times less than the numbers reported in the US.

Large differences exist among European countries, with a six-times higher risk in Ireland and a two-fold higher risk in the UK compared with the average of the other countries.

Several paracetamol overdoses are closely related to suicide attempts, but also unintentional or cumulative overdosing can occur, usually caused by a misuse of the drug, even when therapeutic doses are administered. Many cases of paracetamol poisoning are also due to the use of paracetamol combination products such as acetylsalicylic acid, codeine, oxycodone, propoxyphene, caffeine, dextromethorphan, antihistamines, and decongestants¹².

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 drugs¹³.

Identification of paracetamol overdose is critical, since significant morbidity and mortality may be prevented with early diagnosis and subsequent therapy. Many intoxicated subjects have only minimal and non-specific symptoms which can be mistaken for viral prodrome. These symptoms include malaise, nausea with or without vomiting, and abdominal pains.

Poor prognostic signs include multi-organ failure, which may involve cerebral oedema, renal failure, profound hypoglycemia and lactic acidosis, any signs of which should prompt an immediate liver transplant evaluation¹⁴.

Recent studies on paracetamol hepatotoxicity eventually leading to fatalities together with the studies describing other side effects are here reviewed.

Materials and Methods

The selection of appropriate scientific articles was performed through the following research engines: Cochrane Central, EMBASE, Medline, Science Direct, Scopus, Web of Science, up to November 2016 using the following keywords: “paracetamol”, “adult”, “paediatric”, “hepatotoxicity”, “fatalities”, “side effects” and “liver toxicity”. The sources initially found were screened to exclude papers not suitable for the purpose of the review and duplicate sources. Papers were selected independently by three co-authors and included if selected at least by two of them.

Paracetamol Mechanism of Action

Paracetamol is used worldwide for its analgesic and antipyretic actions. It has a spectrum of action similar to that of non-steroidal anti-inflammatory drugs (NSAIDs) and particularly resembles the cyclooxygenase type 2 (COX-2) selective inhibitors. Paracetamol is on average a weaker analgesic than NSAIDs or COX-2 selective inhibitors, but it is often preferred because of its better gastric tolerance. Despite the similarities to NSAIDs, the mode of action of paracetamol has been not completely clarified, but it is now generally accepted that it inhibits cyclooxygenase type 1 (COX-1) and COX-2 through metabolism by the peroxidase function of these isoenzymes¹⁵. This results in the inhibition of phenoxyl radical formation from a critical tyrosine residue, essential for the activity of COX-1 and COX-2 and prostaglandin (PG) synthesis¹⁶. Paracetamol shows selectivity for inhibition of the synthesis of PGs and related factors, when low levels of arachidonic acid and peroxides are available. Conversely, the drug shows little activity at substantial levels of arachidonic acid and peroxides. The result is that paracetamol does not suppress the severe inflammation of rheumatoid arthritis and acute gout, but it inhibits the lesser inflammation resulting from e.g. the extraction of teeth¹⁶. Unlike both non-selective NSAIDs and selective COX-2 inhibitors, paracetamol inhibits other peroxidase enzymes including myeloperoxidase. Inhibition of myeloperoxidase involves the paracetamol oxidation and the concomitant decreased formation of halogenating oxidants (e.g. hypochlorous acid, hypobromous acid) that may be associated with multiple inflammatory pathologies including atherosclerosis and rheumatic diseases. Therefore, according to this mechanism, the development of these diseases is slowed down. As in the case

of NSAIDs, the analgesic effect of paracetamol is reduced by the inhibitors of many endogenous neurotransmitter systems including serotonergic, opioid, and cannabinoid systems¹⁷.

Hepatotoxicity of Paracetamol and Related Fatalities

After the administration of an oral dose, paracetamol is rapidly absorbed by the intestine, because of its weak acidity and lipid-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 (CYP2E1, CYP2A6) into a reactive metabolite, N-acetyl-para-benzo-quinone imine (NAPQI), that is primarily related to paracetamol hepatotoxicity¹⁴. About 2% of paracetamol is excreted in urine unchanged¹⁸ (Figure 1).

The cellular damages caused by NAPQI are directly related to the dose of paracetamol consumed. In the case of non-toxic consumption, NAPQI is rapidly conjugated by hepatic glutathione, through glucuronidation and sulfonation reactions, to form mercaptate and cysteine complexes, that are eliminated with urine. Differently, if paracetamol is ingested at hepatotoxic doses, the majority of the drug is metabolized by CYP2E1 pathway resulting in glutathione depletion, by activation of GST-S-transferases, and with the build-up of NAPQI at toxic concentrations^{19,20}. The presence

of NAPQI in excessive quantities together with its ability to bind the sulfhydryl groups on cysteine and lysine residues of the hepatocytes mitochondrial proteins also results in decreasing the mitochondrial respiration, an increase of oxidative stress and in mitochondrial dysfunction with ATP stores depletion^{14,19}.

Another hepatotoxicity mechanism involves the formation of peroxy-nitrite, a toxic free radical produced in the mitochondria, from a superoxide and nitric oxide reaction; by causing oxidative injuries, it is responsible for the DNA fragmentation and is directly connected to the cessation of ATP synthesis^{19,21}.

Therefore, the massive presence of NAPQI causes mitochondrial GSH depletion, the formation of proteins adducts, with severe damages to mitochondrial functions and the arrest of ATP production. All these modifications lead to a homeostasis alteration, an increase in the permeability of the cell membrane with a consequent cellular swelling, karyolysis, vacuolization and the loss of cellular elements (as alanine aminotransferase, ALT), which represent one of the biochemical evidence of hepatocytes necrosis^{19,22}.

Repeated suprathreshold misuse, non-intentional misuse, and intentional ingestion may all result in hepatic toxicity.

Paracetamol hepatotoxicity is the main cause of acute liver failure (ALF) in the United States and Europe, with more than 300,000 admissions to the hospital each year in the US alone. About 42% cases of ALF are attributable to paracetamol overdo-

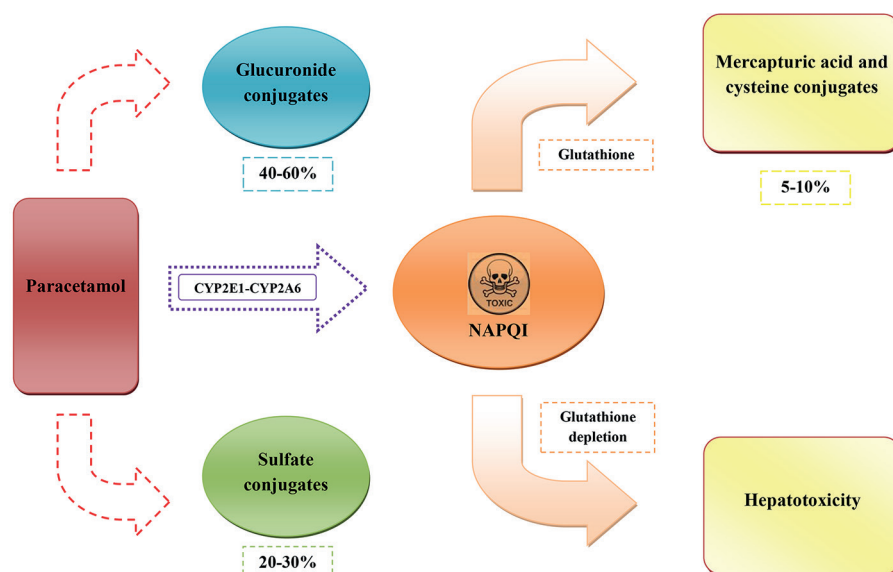


Figure 1. Paracetamol metabolism.

ses^{23,24}, while about 63% paracetamol-related liver toxicity cases are caused by unintentional harmful dosage induced by medications containing paracetamol in combination, primarily those of opioids used for the treatment of chronic pain²⁵.

In the last two decades, several fatalities have been registered in the USA, Europe and Australia in adults and children. Low rates of hepatotoxicity were registered in Asian patients with paracetamol overdose. Mortality and morbidity were non-existent despite high doses of paracetamol ingestion and delayed hospitalization²⁶.

In fatal cases, in which paracetamol induced fulminant hepatic failure, the most frequent causes of death are cerebral oedema or sepsis, in the early phase, and multiorgan failure later.

In patients who develop fulminant hepatic failure or who are otherwise expected to die from liver failure, the mainstay of management is liver transplantation²⁷. The mortality rate from paracetamol overdose increases two days after the ingestion, reaches a maximum on day four, and then gradually decreases. Metabolic acidosis is the most important single indicator of probable mortality and the need for transplantation²⁸.

In a study carried out on twenty-one paracetamol users who died without undergoing liver transplantation²⁹, significant cerebral oedema was present in thirteen individuals and absent in eight. The patients without cerebral oedema had a lower arterial pH on admission, a shorter interval between overdose and death than patients with cerebral oedema. The cause of death in patients without cerebral oedema was predominantly cardiovascular collapse with rapidly progressive resistant hypotension and/or cardiac arrest.

Although, most paracetamol fatalities have been related to hepatic failure due to massive centrilobular necrosis associated with renal tubular necrosis, in recent years a number of cases have been reported pointing to a role played by heart toxicity, as highlighted in cases of myocarditis and fatalities with relatively unimportant concurrent liver damage or time patterns which were inconsistent with death by liver toxicity³⁰.

Finally, a fatal case of paracetamol consumption with liver and renal damage has been reported, and it highlights an atypical isolated skin eruption with significant phenomena of epidermolysis, rhabdomyolysis, disseminated intravascular coagulation and myocardial ischemia. All these delayed the correct diagnosis and rose the question of reviewing the known spectrum of the adverse side effects of paracetamol⁷.

Unintentional overdose with paracetamol in children is relatively common, primarily because the drug is used worldwide in paediatrics.

Young children can unintentionally suffer paracetamol overdose in two ways: firstly, by taking an unsupervised single large dose; secondly as a result of chronic exposure over one or more days to excessive doses³¹.

For example, in 2008, the National Poison Centre in Dunedin New Zealand fielded 806 calls regarding paracetamol poisoning in children, with similar results reported in the USA³². A recent study in the United Kingdom noted that most of the prescriptions for this drug in children is off-label and overdosing was relatively frequent in young children³³. While the hepatotoxic effects of the drug have been well recognized in cases of acute overdose and chronic supratherapeutic doses, the toxic effects are rarely documented in cases where therapeutic guidelines are followed, e.g. an 8-month-old boy underwent a cleft palate repair and placement of bilateral myringotomy tubes. He received paracetamol for routine postoperative pain management and was tolerating liquids and discharged home on postoperative day 1. On day 3, the child was profoundly lethargic with multiple episodes of emesis and was taken to the emergency department, after 4 days his metabolic acidosis, and acute hepatitis started to regress, and he was discharged without any surgical intervention on day 15³⁴.

Although children can be more exposed to an overdose of paracetamol, toxic exposures are rare in neonates, however they may occur via the placenta, resulting from intentional ingestion of overdoses of paracetamol by mothers in the hours preceding delivery³⁵, or by oral³⁶ or intravenous dosing errors in the order of 10 times the therapeutic dose, or finally due to orally repeated doses³⁷. Recently a case of a 26-day-old male admitted to emergency with intestinal bleeding, shock signs, slight liver enlargement, coagulopathy, metabolic acidosis, hypoglycemia, increased serum aminotransferase activity and hyperbilirubinemia after receiving oral paracetamol (10 mg/kg/dose every 4 hours) for three consecutive days, has been described³⁸. It is important to highlight that paracetamol pharmacokinetics and pharmacodynamics in neonates and infants differ substantially from those in older children and adults. Despite the reduced rates of metabolism of the P450 CYP2E1 enzyme and the increased ability to synthesize glutathione which provides greater resistance after overdose, it is possible to produce hepatotoxic metabolites (N-acetyl-p-benzoquinone) that

cause hepatocellular damage, if glutathione sources are depleted. Paracetamol clearance is reduced and the half-life of elimination is prolonged. Therefore, a particular dosing regimen should be followed due to the toxicity risk of cumulative doses. This report highlights the risk of severe hepatotoxicity in neonates taking paracetamol multiple doses for more than two to three days.

As reported by Doyon¹², paracetamol is commonly sold combined with antihistamines, decongestants, dextromethorphan, caffeine, and/or aspirin in over-the-counter (OTC) preparations. Furthermore, there are combinations with opioids or with butalbital/caffeine in preparations to be dispensed after medical prescription.

In its annual report, the American Association of Poison Control Centers reported that paracetamol combination products were involved in 48% of paracetamol-associated fatalities³⁹. The most harmful combination products which cause the majority of deaths are paracetamol/opioid. Conversely, the combination product most involved in suicides is paracetamol/diphenhydramine. Fatal overdoses involving paracetamol combination products reported to US poison centres are on the rise. After the examination of 337 deaths resulting from ingestion of paracetamol combination products reported to US poison centres, it emerged that the ingredient responsible for death was paracetamol itself and not the combination products.

Other Side Effects of Paracetamol

Paracetamol-induced liver necrosis has been studied extensively, but the extrahepatic manifestations 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 adolescents⁴⁰.

The pathophysiology of renal toxicity in paracetamol poisoning has been attributed to cytochrome P450 although other mechanisms have been elucidated, including the role of prostaglandin synthetase and N-deacetylase enzymes. Paradoxically, glutathione is considered an important element in the detoxification of paracetamol and its metabolites; however, its conjugates have been implicated in the formation of nephrotoxic compounds⁴¹. When significant paracetamol-induced hepatotoxicity occurs, a renal injury is also commonly seen. Several case reports have attempted to define patients characterized by an increased

risk of paracetamol-induced nephrotoxicity. Although the data are limited, it is reasonable to assume that patients with a nephrotoxicity risk may be similar to those at risk for hepatotoxicity, i.e. patients with depleted glutathione due to starvation, fasting, or alcoholism⁴².

Some studies suggest that paracetamol has an adverse cardiovascular safety profile⁴³ and because this substance has been shown to inhibit COX-2, it has the potential to increase blood pressure and promote thrombosis.

Since traditional non-steroidal anti-inflammatory drugs have been associated with an increased risk of acute cardiovascular events, current guidelines recommend acetaminophen as the first-line analgesic of choice on the assumption of its greater cardiovascular safety. However, 33 patients with coronary artery disease included in a randomized, double-blind, placebo-controlled, crossover study, received acetaminophen (1 g) on top of standard cardiovascular therapy for 2 weeks. This study demonstrated for the first time that paracetamol induces a significant increase in ambulatory blood pressure in patients with coronary artery disease. Thus, the use of paracetamol should be evaluated as rigorously as traditional non-steroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors, particularly in patients at increased cardiovascular risk⁴⁴.

Conclusions

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 formulations¹⁹.

Because of soaring cases of hepatotoxicity related to abuse/misuse of paracetamol, the US Food and Drug Administration (FDA) in 2009 asked for the elimination of drugs containing paracetamol-related products (FDA 2009). Subsequently, in 2011, the US FDA established that all medications containing paracetamol in combination should not exceed 325 mg of paracetamol per tablet^{24,25}.

Thus, since January 2014, after the ratification of the FDA's decision, more than half of pharmaceutical manufacturers voluntarily limited the amount of paracetamol, in paracetamol related products, to no more than 325 mg for each tablet⁶. However, some combination drug medications

containing more than 325 mg of paracetamol are still commercially available⁴⁵. US FDA has declared that it is crucial that the packages have labels with information about the risk of liver damage caused by the overuse of the drug; moreover it is essential to use only its international name and not the two different names of the same drug (paracetamol or acetaminophen) because it could mislead the patients; in fact, if not properly informed, the unaware patient can ingest the same substance under different names¹⁵.

Nevertheless, today in the US the number of paracetamol overdose related deaths, intentional or unintentional, is still very high, averaging about 500 victims per year; for this reason, a new legislation informing more clearly about the administration of paracetamol, packaging and selling and its combination with other drugs, especially with opioid analgesics, is currently highly needed^{46,47}. The most drastic proposal suggested by FDA is the withdrawal of all complex drugs, both available over the counter (OTC) and by prescription, because as the various studies indicate, they are responsible to a great degree for acute paracetamol poisoning.

Since paracetamol is responsible for nearly half the cases in the US of acute liver failure and remains the leading cause of liver transplantation, continued awareness promotion, education and research should be undertaken¹⁹.

Conflict of interest

The authors declare no conflicts of interest.

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