

Paracetamol Toxicity: A Review

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Abstract

One of the most important discoveries in field of medicine was synthesis of acetaminophen (Paracetamol) which is one of the most commonly used medications worldwide. Paracetamol which is commonly used as analgesic and antipyretic shows some strange and life threatening effects like liver damage which leads to fulminant liver failure and also death. Paracetamol is now the most common drug in self-poisoning, with a high rate of morbidity and mortality. Various steps are taken by regulatory authorities across the world to forestall the drug related toxicity. The recommendations for reducing the risk would be to educate the caregivers about the potential for toxicity. The dosing guidelines based on age and weight should be reviewed by the physician during each visit. The drug regulatory authority in India should respond immediately by taking an action that results in the decline of toxicity cases. In view of the potential for harm, serious consideration should be given to changing the legal status of Paracetamol, possibly to a prescription-only medicine.

Key words: Hepatic Damage, Paracetamol, Paracetamol Toxicity, Paracetamol Poisoning

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Introduction

Paracetamol (acetaminophen) was discovered 100 years ago, but its use as an over-the-counter (OTC) medication began only in the 1960s and is now the most frequently used OTC medication.^[1] Paracetamol overdose is a common means of self-poisoning worldwide due its wide availability and accessibility.^[2] It is widely available as a single-component medication and also as a component of a plethora of combination over-the-counter and prescription medications. Despite its safety when used properly, Paracetamol poisoning is one of the more common overdoses reported to poison centers. In 2009, the American Association of Poison Control Centers' National Poison Data System reported 401 deaths caused by Paracetamol or an Paracetamol combination product.^[3] Paracetamol-induced liver failure is now the leading cause of acute liver failure and is the second most common cause of liver failure requiring transplantation in the United States.^[4] However, it is important to view the entire picture and consider that this number is relatively small, considering the massive amount of acetaminophen that is used. But

regardless of the magnitude of the problem, both unintentional and intentional acetaminophen overdose remains a serious public health concern. Keeping this in view the present article aims to put forward the toxicity caused by Paracetamol and ways to tackle this issue.

History

Harmon Northrop Morse first synthesized Paracetamol via the reduction of P-nitrophenol with Tin in glacial acetic acid in 1878; however, Paracetamol was not used in medical treatment for another 15 years. In 1893, Paracetamol was discovered in the urine of individuals who had taken Phenacetin. In 1899, Paracetamol was found to be a metabolite of acetanilide. In 1948, Brodie and Axelrod determined that the analgesic effect of acetanilide was due to its active metabolite Paracetamol. The product was then first sold in 1955 by McNeil laboratories for relief of pain and fever in children, under the brand name Tylenol children's elixir.^[5]

Epidemiology of Toxicity

The number of liver failure cases in India, due to Paracetamol toxicity is less when compared

with that of the western countries this may be a consequence of under-reporting. United States outstands every other country by reporting a whopping number of ALF (Acute Liver Failure) cases. It is reported that there were an estimated 56,000 emergency room visits, 26,000 hospitalizations, and 458 deaths related to acetaminophen-associated overdoses per year during the 1990-1998 period.^[6] In 2007, 1600 ALF cases were reported in the U.S out of which the majority cases had Paracetamol as the underlying pathophysiology. In U.K Paracetamol accounts about 50% of self-poisoning cases causing around 200 deaths every year.^[7] The drug induced toxicity is less in numbers in children but not completely absent. The drug shows no age discrimination. The morbidity and mortality is found to be less in countries which limits the sale of Paracetamol on a single purchase.^[8,9]

Etiology and Pathophysiology of Paracetamol Toxicity

Paracetamol is metabolized in the liver via three pathways-glucuronidation, sulfation or via the hepatic cytochrome P450 enzyme system. The toxic effects of Paracetamol are due to alkylating metabolite *N*-acetyl-*p*-benzo-quinone imine (NAPQI).^[10] When acetaminophen is ingested in therapeutic amounts, approximately 90% of the parent compound undergoes a combination of sulfate and glucuronide conjugation.^[10] These conjugates are eliminated as nontoxic metabolites.^[11,12,13] An additional 5% is excreted in the urine. A small fraction (~4%-5%) is metabolized by the cytochrome P450 system mixed function oxidase system, primarily by enzyme CYP2E1, to a highly reactive and toxic metabolite, *N*-acetyl-*p*-benzoquinone imine (NAPQI). Endogenous glutathione in the liver serves as a substrate for NAPQI, resulting in the production of a nontoxic metabolite, mercapturic acid, which is excreted in the urine. However, when an overdose occurs, the normal metabolic pathways become saturated and more acetaminophen is shunted through the P450 system. Consequently, more NAPQI is produced and when glutathione is depleted by 70%, the excessive amounts of NAPQI bind to hepatocytes, causing cellular

toxicity, which is manifest as hepatic necrosis.^[14]

Clinical Course

The clinical features of acetaminophen toxicity that result from hepatic necrosis can be divided into 4 stages.^[10] During the first few hours the patient may be relatively asymptomatic; but the clinical course evolves over 24 hours and the gastrointestinal symptoms like nausea, abdominal pain and vomiting predominate. In the second stage (12 to 48 hours postingestion) the gastrointestinal discomfort may resolve, but subclinical hepatotoxicity progresses and begins to express itself. Abdominal pain may reappear and the patient may complain of right upper quadrant tenderness. Laboratory values begin to show evidence of hepatotoxicity—liver function tests such as the aspartate (AST) and alanine transaminase (ALT) increase dramatically, there is also increase in the international normalized ratio (INR), which reflect the severity of the underlying pathology. During the latter part of stage 2, the AST and ALT are near peak values. In stage 3 (48 to 96 hours), as liver injury accelerates, the following signs of hepatic failure become grossly apparent: bleeding, encephalopathy, jaundice, acidosis, renal failure. If the patient survives the pathophysiological insults of stage 3, they will progress to the final stage, that of recovery.^[11,12,13]

Dosage

The recommended dose for oral or rectal Paracetamol in symptomatic fever (temperature > 38.5°C) is 15 mg/kg every 6 h (≤60 mg/kg/day),^[15] whereas the recommendation for analgesia is 15 mg/kg every 4–6 hourly, up to a maximum of 60–90 mg/kg/day for oral dose and the rectal dose being 20 mg/kg/dose every 6 hourly, up to a maximum of 90 mg/kg/day.^[15] A sustained administration of supratherapeutic doses of Paracetamol (>90 mg/kg/day) to a sick child younger than 2 years for more than 1 day has been identified as a significant risk for hepatotoxicity, whereas in acute ingestion of Paracetamol a higher dose of 150 mg/kg is associated with toxicity.^[16]

Measures of Toxicity Prevention by Regulatory Authorities

USFDA (US) ^[17]

1999: Issued a regulation for all the Paracetamol manufactures to include an alcohol warning label

2002: Advised a distinctive labeling and specific liver toxicity warning.

2004: Launched a patient education campaign.

2007-2009: Launched a working group to identify the toxicity epidemiology on the use of over the counter (OTC) products.

2011: Advised the manufacturers to reduce the strength of Paracetamol to 325mg in a combination. It also proposed a guideline for reducing the daily maximum dose from 4g to 3g. It also advised the manufacturers to include a 'Black Box' warning. ^[18,19]

MHRA (UK) ^[20]

1999: Laid down a legislation that resulted in decrease in the number of tablets of Paracetamol and salicylates to 16 in supermarkets and 32 in the pharmacies.

D.C.G.I (India)

2003: DCGI insisted all the manufacturers to include a mandatory warning statement on the packs of Paracetamol. ^[21]

2007: DCGI banned a number of Paracetamol combination drugs like Paracetamol + alprazolam, Paracetamol + analgin, chlorzoxazone + ibuprofen + Paracetamol + diclofenac + oxyphenbutazone + magnesium hydroxide. ^[22]

2011: DCGI made it mandatory for all manufacturers of Paracetamol combination drugs to put a box-label on the formulation packs, warning the patient-consumer of potential liver toxicity if the drug is consumed more than the recommended daily dose. ^[23]

2013: The office of DCGI addressed to all State Drugs Controllers that lowering of the Paracetamol content to 325 mg is applicable to the combination of the Paracetamol with other analgesic/anti-inflammatory drugs. ^[24]

Considering that an overdose of one of the most common fever and pain-reducing drugs - Paracetamol - may lead to liver damage, the US Food and Drug Administration (FDA) has limited its dose to 325 mg when given in

combination with non-steroidal anti-inflammatory drugs (NSAIDs), which are known to have an adverse effect on the liver. Under FDA regulations, Paracetamol is allowed to be combined with only aspirin and opioids. But in India, several potentially harmful combinations have been approved containing 500 mg or more of Paracetamol with NSAIDs, experts pointed out."For example, Paracetamol is available in combination with Nimesulide, Piroxicam, Etodolac, Lornoxicam and Dexibuprofen. There are several products available in markets which are sold as OTC products contain Paracetamol 500mg as D-cold tablets, Vicks action 500. Indian experts have called for a review of pain and fever-reducing combination drugs marketed in the country following an advisory by US regulatory authorities that limits Paracetamol dosage when given in combination with other drugs.

Conclusion

Paracetamol is widely used as drug of choice for fever and analgesia. It is available as OTC in a variety of combinations and strength. An easy availability over the counter, several preparations with varying drug doses, overzealous usage to suppress fever and its inadvertent use with the notion of being a safe drug contribute to therapeutic misadventure. Though the epidemiology of liver failure on using the drug in India is less, it is the responsibility of the manufacturer to include proper labeling and directions for the effective use of the product. The recommendations for reducing the risk would be to educate the caregivers about the potential for toxicity. The dosing guidelines based on age and weight should be reviewed by the physician during each visit. The drug regulatory authority in India should respond immediately by taking an action that results in the decline of toxicity cases. Country wide education campaign can be competent. Since the effective measures prove a considerable reduction morbidity and mortality, they should be immediately put down by the government to prevent more number of people falling under the risk of liver failure.

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