ISO 9001 - 2015

ISSN 2349 - 4891

Monthly

IJRRAS

IF
4.665

Volume 4,Issue 9, September 2017

International Journal of

Recent Research and Applied Studies

SURRAGH PUBLICATIONS

ISSN: 2349 - 4891

International
Journal of Recent Research and Applied Studies
(Multidisciplinary Open Access Refereed e-Journal)

Acetaminophen (Paracetamol) Drug Overdose Toxic Effect on Human Health

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Received 10th August 2017, Accepted 19th September 2017

Abstract

Acetaminophen (Paracetamol) is single of the most generally used pain-relieving and antipyretic drugs in the world. Drugs are easily available in the market without a recommendation. Paracetamol it decreases fever and pain, it is found extremely toxic. The drug mechanism of action in reduces fever and pain. Specifically when is taken commonly and in high doses there is a risk of hazardous health effects A large number cases in accidental exposures and deliberate Suicide incidents take in paracetamol, every year, has seen increasing number of recorded cases of paracetamol-induced liver intoxication all over the world. Paracetamol toxicity effects like Liver harmfully effect to live failure and death.

Keywords: Paracetamol, Drugs, Effects, Toxic.

Introduction

The analgesic and antipyretic properties of paracetamol were first described in 1893 [1]. 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 [2]. One among them is Paracetamol which we often use to get relief from fever, headache and certain pains such as muscle aches, arthritis, backache, toothache and cold. But Paracetamol shows some strange and life threatening effects i.e., causing liver damage which leads to fulminant liver failure and also death. Paracetamol or acetaminophen is an active metabolite of phenacetin. Unlike aspirin, Paracetamol is not a very effective anti-inflammatory agent. It is well tolerated, lacks many of the side effects of aspirin and is available over-the-counter, so it is commonly used for the relief of fever, headache and other minor aches and pains. Paracetamol is also useful in the management of more severe pains, where it allows lower dosages of additional Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) or opioid analgesics to be used, thereby minimizing overall side-effects. It is a major ingredient in numerous cold and flu medications, including Tylenol and Panadol, among others. It is considered safe for human use at recommended doses; however acute overdose can cause fatal liver damage, often heightened with use of alcohol and the number of accidental self-poisoning and suicides has grown in recent years [3]. Because the drug may not be equally distributed throughout the suppository, the practice of dividing a suppository may not provide a predictable dose. In addition, different rectal preparations have substantially different absorption characteristics that cause variation in bioavailability [4]. In India, the data on paracetamol self poisoning is uncommon and it is insufficient as compared to that of the west. A 10 year retrospective hospital based study reported 0.32% cases of acute paracetamol overdoses due to accidental exposures [5].

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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 [6]. 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 [7]. 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 [8]. Pediatric paracetamol exposures account for approximately 30,000 reports to the National Poison Data System annually in

United States [9]. 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 [10]. It has also become increasingly common in countries like Denmark and Australia [11,12]. In Scotland, the rate of paracetamol overdose increased almost 400%between 1981–83 and 1991–93 [13]. Paracetamol toxicity primarily manifests in the liver, and paracetamol overdose is the most common apparent cause of acute liver failure in the UK and Western countries. Paracetamol poisoning in the paediatric age group can be divided into three major groups with differing demographic and clinical characteristics. These are intentional self-poisoning, accidental paediatric ingestion and poisoning due to repeated supratherapeutic dosings of paracetamol. Rumack and Matthew's landmark review in 1975 brought attention to paracetamol poisoning in children. In 1984, Rumack described a cohort of 417 children, aged 5 years or younger, who had ingested potentially toxic amounts of paracetamol. Only three children had altered liver enzymes and all recovered with treatment with no fatalities in the cohort. Thus, it was accepted that in general, young children with accidental single exposures to paracetamol overdoses were less at risk of developing toxic reactions and subsequent morbidity and mortality than adolescents or adults [1].

Mechanism **Works**

Although paracetamol was discovered over 100 years ago and has been widely used in medical practice for more than half the century, its mechanism of action has not been elucidated until now [14]. It has analgesic and antipyretic properties similarly to NSAIDs, but contrary to them, it does not possess any anti-inflammatory activity. When applied in recommended doses, it does not induce typical for NSAIDs gastrointestinal side effects. However, it suppresses prostaglandin production likewise NSAIDs. Due to lack of an anti-inflammatory component, paracetamol has not been regarded as a member of the NSAIDs family in pharmacological textbooks, although what is interesting, it has been always discussed together with these drugs. Therefore, the discussion on the mechanism of action of paracetamol should begin from the analysis of NSAIDs action [15]. Paracetamol reduces fever and pain is still a source of considerable debate. The reason for this confusion has largely been due to the fact that Paracetamol reduces the production of prostaglandins and other pro-inflammatory chemicals. Further research has shown that Paracetamol modulates the Endogenous Cannabinoid System (ECS) [16]. Paracetamol is metabolized to AM404 which inhibits the uptake of the endogenous cannabinoid/vanilloid anandamide by neurons. Anandamide uptake would result in the activation of the main pain receptor (nociceptor) of the body. Also AM404 inhibits sodium channels as like anesthetics, lidocaine and procaine [17]. Either of these actions by themselves has been shown to reduce pain and is suggested that its pain-relieving action is indeed mediated by the ECS [18].

Paracetamol Drug Metabolism

The liver via three pathways-glucuronidation, sulfation or via the hepatic cytochrome P450 enzyme system, which is responsible for the toxic effects of Paracetamol due to alkylating metabolite N-acetyl-P-benzo-quinone imine (NAPQI) [19]. In this pathway, Paracetamol is converted to a metabolite which is toxic to liver cells. Glutathione (a tripeptide) then binds to this toxic metabolite resulting in a non-toxic compound. Hepatotoxicity occurs when glutathione stores are depleted faster than they can be regenerated and the toxic metabolite is left to accumulate. The metabolism of Paracetamol is an excellent example of intoxication [3].

Minimum toxic dose

Although Rumack and Matthew did not specify a minimum level of toxicity, it was generally agreed following their work that a minimum single dose of 150 mg/kg may be associated with hepatocellular damage. Other studies have supported this dose as being the threshold for toxicity. Hepatocellular injury was associated with reported doses in excess of 150mg/kg/day at an odds ratio of 18 compared to doses below 150 mg/kg/day (95% CI, 2e139). However, a minimum toxic dose level of paracetamol has not been conclusively established. Firstly, it is difficult to accurately document the ingested dose as well as the time of ingestion in many cases, especially in young children due to recall issues and numerous different formulations. Secondly, the dosing picture may be complicated by repeated ingestions rather than a single overdosing as discussed earlier. Thirdly, alterations in the individual metabolism of patients can interfere with efforts to determine dose-response relationships. Fasting and malnutrition, alcohol ingestion, drug interactions or concomitant medical disorders such as viral illnesses, hepatic disease or surgery can all influence drug metabolism [1].

Toxicity of Paracetamol Drug

'Paracetamol hepatotoxicity,' which mainly results into liver injury but is also one of the most common causes of poisoning all over world. Many people who develop Paracetamol toxicity may feel no symptoms at all in the first 24 hours that follow overdose of Paracetamol. Others may initially experience nonspecific complaints like vague abdominal pain and nausea. As the Paracetamol toxicity increases, signs of liver failure like low blood sugar; low blood pH, easy bleeding, and hepatic encephalopathy may develop. Timely treatment can cure the condition of the patient but untreated cases may result in death. Often a liver transplant is needed if damage to the liver gets severe. The risk of Paracetamol toxicity increases with excessive alcohol intake, fasting or anorexia nervosa, and also with

the use of certain drugs like isoniazid [3]. Events that produce hepatocellular death following the formation of acetaminophen protein adducts are poorly understood. One possible mechanism of cell death is that covalent binding to critical cellular proteins results in subsequent loss of activity or function and eventual cell death and lysis. Primary cellular targets have been postulated to be mitochondrial proteins, with resulting loss of energy production, as well as proteins involved in cellular ion control [20]. Tirmenstein and Nelson, reported alterations of plasma membrane ATPase activity following toxic doses of acetaminophen [21, 22].

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 [23]. 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) [23,24]. 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 [25-28] Overall, renal insufficiency occurs in approximately 1-2% of patients with paracetamol overdose [29]. 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 [25]. 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 [30]. Tubular swelling with loss of the tubular brush border and distortion of mitochondrial organization are often seen on electron microscopy [31].

Paracetamol Hepatotoxicity and Its Interactions with Alcohol Consumption

It is claimed that chronic alcoholics are at increased risk of Paracetamol (acetaminophen) hepatotoxicity not only following overdosage but also with its therapeutic use. Increased susceptibility is supposed to be due to induction of liver microsomal enzymes by ethanol with increased formation of the toxic metabolite of Paracetamol. However, the clinical evidence in support of these claims is anecdotal and the same liver damage after overdosage occurs in patients who are not chronic alcoholics. Many alcoholic patients reported to have liver damage after taking Paracetamol with 'therapeutic intent' had clearly taken substantial overdoses. The Paracetamol-alcohol interaction is complex; acute and chronic ethanol has opposite effects. In animals, chronic ethanol causes induction of hepatic microsomal enzymes and increases Paracetamol hepatotoxicity as expected (ethanol primarily induces CYP2E1 and this isoform is important in the oxidative metabolism of Paracetamol). However, in man, chronic alcohol ingestion causes only modest (about two fold) and short-lived induction of CYP2E1, and there is no corresponding increase (as claimed) in the toxic metabolic activation of Paracetamol. Acute ethanol inhibits the microsomal oxidation of Paracetamol both in animals and man. This protects against liver damage in animals and there is evidence that it also does so in man. The protective effect disappears when ethanol is eliminated and the relative timing of ethanol and Paracetamol intake is critical. The belief about the hepatotoxicity of Paracetamol in people who drink alcohol regularly is shared by the USA Food and Drug Administration (FDA) which now requires that Paracetamol sold in the USA be labeled with the warning stating that, 'If you consume 3 or more alcoholic drinks every day, you should ask your doctor whether you should take Paracetamol (acetaminophen) or other pain relievers/fever reducers. Acetaminophen may cause liver failure'. Canada also has issued a warning about the liver damage in heavy users of alcohol who take more than the recommended dose of Paracetamol. Hepatotoxicity from therapeutic doses of Paracetamol is unlikely in patients who consume moderate to large amounts of alcohol daily. However, patients with severe alcoholism should be instructed or supervised about the correct dosage of Paracetamol. The depression often associated with alcoholism may make them more likely to take an overdose of Paracetamol [32]. In many of the reports where it is alleged that Paracetamol hepatotoxicity was enhanced in chronic alcoholics, the reverse should have been the case because alcohol was actually taken at the same time as the Paracetamol. Chronic alcoholics are likely to be most vulnerable to the toxic effects of Paracetamol during the first few days of withdrawal but maximum therapeutic doses given at this time have no adverse effect on liver function tests. Although the possibility remains that chronic consumption of alcohol does increase the risk of Paracetamol hepatotoxicity in man (perhaps by impairing glutathione synthesis), there is insufficient evidence to support the alleged major toxic interaction [33]

Discussion

Paracetamol poisoning is the most common poisoning presenting to health services. Paracetamol is strong pain killer for the hangover headache may damage liver. The vast commonly of solo paediatric unintentional ingestions will require no treatment. Paracetamol drug events related with oral acetylcysteine include nausea and vomiting. Studies shows in human and animal body shown that paracetamol overdose may lead to renal dysfunction and liver failure. Paracetamol drugs does not irritate the inside layer of stomach, effect blood coagulation or effect kidney function. Paracetamol is given orally, a loading dose can reduce the time required to accomplish therapeutic levels. Mostly peoples are swallow less than 30 g of paracetamol, with only a minor proportion of overdoses consuming a paracetamol absorption greater than dual the nomogram line. It must be think of that even with the fact that paracetamol has a wide clinical presentation it is not a drug devoid of side effects.

Conclusion

The most frequently conveyed adverse effects of Paracetamol arterial acetylcysteine are anaphylactoid responses, counting rash, pruritus, angio-oedema, tachycardia, hypotension and bronchospasm. The adverse effects happen with the specious dosing of intravenous acetylcysteine in human . These adverse effects contains cerebral oedema and hyponatraemia. They are rare information of deaths which were affected due to anaphylactoid responses. Peoples with an acute absorption look less vulnerable to toxicity. Peoples who intentionally take highdoses, late presenters, humans who want swallowed several supratherapeutic doses, as well as humans with comorbidities taken enzyme-inducers or are underweight are more at danger of hepatocellular destruction.

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