

Beware of Paracetamol Toxicity

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Abstract

The Effect of Paracetamol mechanism by which it works, metabolism, recommended doses, toxic dosage are discussed with study reports in this paper. Paracetamol shows some life threatening effects like Liver damage which in turn leads to live failure and death. Though it reduces fever and pain, it is found highly toxic. The mechanism by which Paracetamol reduces fever and pain is still not known. On metabolism, Paracetamol is converted to a metabolite which is very toxic to liver cells. In recommended doses (1-2 g/day), Paracetamol does not irritate stomach lining, kidney cells and liver cells. Studies reported that high dosage (>2 g/day), resulted in Gastrointestinal complications, abnormal Kidney function, Liver damage.

Keywords: Paracetamol; Phenacetin; Endogenous Cannabinoid System (ECS); Paracetamol Metabolism; Recommended dosage; Toxic doses; Liver failure

Introduction

In our day to day life we are using so many drugs as medicines. We are consuming such medicines unknowing their nature, properties, mechanism of action, toxicity, etc. 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.

History

Its history says that when Cinchona tree became scarce in the 1880s, people began to look for alternatives. Two alternative antipyretic agents were developed in 1880s; Acetanilide in 1886 and Phenacetin in 1887. 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 that had taken Phenacetin and was concentrated into white crystalline compound with a bitter taste. In 1899, Paracetamol was found to be a metabolite of acetanilide. This discovery was largely ignored at that time. 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 as a pain and fever reliever for children, under the brand name Tylenol children's elixir.

Pharmacodynamics of Paracetamol

Paracetamol is a para-aminophenol derivative that exhibits analgesic

and anti-pyretic activity. The mechanism of action is dependent on the inhibition of prostaglandin synthesis in the Central Nervous System (CNS) and peripherally blocks pain impulse generation [1]. It does not possess anti-inflammatory activity. It provides relief from mild to moderate pain and fever.

Paracetamol is metabolised by the liver and excreted in the urine mainly as glucuronide and sulphate conjugates; less than 5% is excreted as unmodified Paracetamol. Binding to the plasma proteins is minimal at therapeutic concentrations [2]. High dose-usage (greater than 2,000 mg per day) of Paracetamol increases the risk of upper gastrointestinal complications like stomach bleeding. Heavy use of Paracetamol (300 grams a year or 1 g per day on average) has been linked to a condition known as 'Small Indented and Calcified Kidneys' (SICK).

A study in 2008 on long term side effects of Paracetamol tablets in children found that administering Paracetamol for fever in the first year of life was linked with an increase in the incidence of asthmatic symptoms at 6-7 years. It also stated that use of Paracetamol (both in the first year of life and in children aged 6-7 years) was associated with an increased incidence of rhinoconjunctivitis and eczema [3].

Hypersensitivity reaction (rashes and shortness of breath), Blood disorders resulting in readiness to bruise or bleed (e.g. thrombocytopenia) or low numbers of white blood cells (leucopenia) a serious allergic reaction to this drug is unlikely, but seek immediate medical attention if it occurs. Symptoms of a serious allergic reaction include: rash, itching/swelling (especially of the face/tongue/throat), dizziness, trouble breathing [4].

The most serious concern with Paracetamol is the effect it has on the liver, and therefore certain things must be attended to immediately. Yellow eyes or skin can be a sign that the liver is damaged due to the ingestion of Paracetamol, and this is most frequently seen with large

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doses or extended periods of use. Bloody urine and stools are also a side effect of Paracetamol and suggest irritation in the stomach [5]. The most common effects of Paracetamol poisoning are nausea and vomiting. These effects usually appear within 24 hours after the medication.

Mechanism by which Paracetamol Works

The mechanism by which 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) [6]. Paracetamol is metabolized to AM_{404} 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 AM_{404} inhibits sodium channels as like anesthetics, lidocaine and procaine [7]. 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 [8].

Paracetamol Metabolism

Paracetamol is metabolized in the liver via three pathways—glucuronidation, sulfation or via the hepatic cytochrome P_{450} enzyme system, which is responsible for the toxic effects of Paracetamol due to alkylating metabolite N-acetyl-P-benzo-quinone imine (NAPQI) [9]. 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.

Paracetamol Hepatotoxicity

Overdose of Paracetamol leads to '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.

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 [10]. Tirmenstein and Nelson, [11] and Tsokos-Kuhn et al. [12] reported alterations of plasma membrane ATPase activity following toxic doses of acetaminophen.

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 [13].

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 [14].

Intravenous vs. Oral Administration of Paracetamol

Paracetamol has previously been available for intravenous use in the form of its pro-drug, propacetamol. Used in France since 1985, propacetamol, provided as a powder for reconstitution, is water soluble and rapidly hydrolysed by plasma esterases to form Paracetamol and diethylglycine; a dose of 1 g propacetamol provides 0.5 g Paracetamol after hydrolysis. In a study of patients undergoing dental extraction, propacetamol was significantly better than placebo for all measured parameters; pain relief, pain intensity, patient's global evaluation and duration of analgesia [15]. Advantages of intravenous Paracetamol over

propacetamol are that it is available in a preformed solution, and it is not associated with pain on injection or contact dermatitis. Paracetamol is bioequivalent to propacetamol [16].

In a study of 35 patients undergoing day-surgery, intravenous propacetamol (the IV prodrug of Paracetamol) reached therapeutic plasma concentrations more quickly and predictably than oral Paracetamol [17]. Paracetamol plasma concentrations were observed for the first 80 minutes after administration of either 1 g or 2 g oral Paracetamol or 2 g intravenous propacetamol. Intravenous Paracetamol provided an average concentration within the therapeutic range after 20 minutes. There was a large and unpredictable variability with oral administration; some patients who received 1 g orally did not achieve detectable plasma levels within the 80 minute study period, and the average plasma concentration after receiving this dose was subtherapeutic throughout. 2 g oral Paracetamol achieved a median plasma concentration within the therapeutic range after 40 minutes, suggesting that when Paracetamol is given orally, a loading dose can reduce the time needed to achieve therapeutic levels.

Dosage and Study Reports

In recommended doses, Paracetamol does not irritate the lining of stomach, effect blood coagulation as much as NSAIDs or effect kidney function. However, studies have shown that high dosage (>2 g/day) does increase the risk of upper gastrointestinal complications [18]. Paracetamol overdose results in more calls to poison control centres in the US than overdose of any other pharmacological substances, accounting for more than 100,000 calls, as well as 56,000 emergency room visits, 2,600 hospitalizations and 458 deaths due to acute liver failure per year [19].

A recent study of cases of acute liver failure between November 2000 and October 2004 by the centres for disease control and prevention (US) found that Paracetamol was the cause of 41% of all cases in adults and 25% of cases in children [20]. In massive overdoses, coma and metabolic acidosis may occur prior to hepatic failure. Paracetamol, particularly in combination with weak opioids is more likely than NSAIDs to cause rebound headache although less of a risk than ergotamine or triptans used for migraines [21].

Toxic dose of Paracetamol is highly variable. In adults, single dose of 150 mg/kg or multiple smaller doses within 24 hours have a reasonable likelihood of causing toxicity and leads to death with a dose as little as 4 g/day. In children, acute doses above 200 mg/kg cause toxicity [22].

Severe diarrhea, increased sweating, loss of appetite, nausea and vomiting, stomach cramps or severe pain, or swelling, tenderness and pain in the upper abdomen could all be signs of a Paracetamol overdose and you should seek medical attention immediately [5]. Without timely treatment, overdose can lead to liver failure and death within days. Paracetamol toxicity is, by far the most common cause of acute liver failure in both the US and the UK [23,24]. It is used in suicide attempts by those unaware of the prolonged time course and high morbidity associated with Paracetamol-induced toxicity in survivors.

Conclusion

Paracetamol, which is believed to be a strong pain killer for the hangover headache may damage liver. Though Paracetamol gives positive results in relieving pain, it is found to be too toxic (as its way of mechanism in relieving pain is still unknown). So always beware of Paracetamol toxicity and should never consume Paracetamol beyond

the recommended dose even if fever or headache is too high or unbearable.

References

1. <http://www.doctorslounge.com/rheumatology/drugs/analgesics/miscellaneous/paracetamol.htm>
2. http://www.gsk.com.au/...ashx/.../Panadol_Osteo_Product_Information.pdf
3. <http://www.pharmaceutical-drug-manufacturers.com/articles/paracetamol-sideeffects.html>
4. <http://drugs.webmd.boots.com>
5. http://www.ehow.com/about_5513450_Paracetamol-side-effects.html
6. Högestätt ED, Jönsson BA, Ermund A, Andersson DA, Björk H, et al. (2005) Conversion of acetaminophen to the bioactive N-acylphenolamine AM404 via fatty acid amide hydrolase-dependent arachidonic acid conjugation in the nervous system. *J Biol Chem* 280: 31405-31412.
7. Kofalvi A (2008) Alternate interacting sites and novel receptors for cannabinoid ligands. *Cannabinoids & Brain* 1: 131-160.
8. Ottani A, Leone S, Sandrini M, Ferrari A, Bertolini A (2006) The analgesic activity of paracetamol is prevented by the blockade of cannabinoid CB1 receptors. *Eur J Pharmacol* 531: 280-281.
9. Borne, Ronald F (1995) Non steroidal anti-inflammatory drugs. Principles of medicinal chemistry (IV).
10. Nelson SD (1990) Molecular mechanisms of the hepatotoxicity caused by acetaminophen. *Semin Liver Dis* 10: 267-278.
11. Tirmenstein MA, Nelson SD (1989) Subcellular binding and effects on calcium homeostasis produced by acetaminophen and a nonhepatotoxic regioisomer, 3'-hydroxyacetanilide, in mouse liver. *J Biol Chem* 264: 9814-9819.
12. Tsokos-Kuhn JO, Hughes H, Smith CV, Mitchell JR (1988) Alkylation of the liver plasma membrane and inhibition of the Ca²⁺ ATPase by acetaminophen. *Biochem Pharmacol* 37: 2125-2131.
13. Garry GG, Kieran FS, Richard OD (2004) Alcohol and Paracetamol. *Aust Prescr* 27: 14-15.
14. Prescott LF (2000) Paracetamol, alcohol and the liver. *Br J Clin Pharmacol* 49: 291-301.
15. Moller PL, Sindet-Pedersen S, Petersen CT, Juhl GI, Dillenschneider A, et al. (2005) Onset of acetaminophen analgesia: comparison of oral and intravenous routes after third molar surgery. *Br J Anaesth* 94: 642-648.
16. Flouvat B, Leneveu A, Fitoussi S, Delhotal-Landes B, Gendron A (2004) Bioequivalence study comparing a new paracetamol solution for injection and propacetamol after single intravenous infusion in healthy subjects. *Int J Clin Pharmacol Ther* 42: 50-57.
17. Holmér Pettersson P, Owall A, Jakobsson J (2004) Early bioavailability of paracetamol after oral or intravenous administration. *Acta Anaesthesiol Scand* 48: 867-870.
18. Garcia RLA, Hernandez DS (2000) Risk of upper gastrointestinal complications. *Arthritis research & therapy* PMID.
19. Lee WM (2004) Acetaminophen and the U.S. Acute Liver Failure Study Group: lowering the risks of hepatic failure. *Hepatology* 40: 6-9.
20. Bower WA, Johns M, Margolis HS, Williams IT, Bell BP (2007) Population-based surveillance for acute liver failure. *Am J Gastroenterol* 102: 2459-2463.
21. Colás Chacartegui R, Temprano González R, Gómez Arruza C, Muñoz Cacho P, Pascual Gómez J (2005) [Abuse pattern of analgesics in chronic daily headache: a study in the general population]. *Rev Clin Esp* 205: 583-587.
22. Dart RC, Erdman AR, Olson KR, Christianson G, Manoguerra AS, et al. (2006) Acetaminophen poisoning: an evidence-based consensus guideline for out-of-hospital management. *Clin Toxicol (Phila)* 44: 1-18.
23. 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.
24. Ryder SD, Beckingham IJ (2001) Abc of diseases of liver, pancreas and biliary system: other cause of parenchymal liver disease. *BMJ* 322: 290-292.