Beware of Paracetamol Toxicity

H.L. Vidhya Malar* and S. Mary Mettilda Bai

P.G and Research Department of Zoology, Holy Cross College, Nagercoil- 629 004. Tamil Nadu. India.
*E-mail: vidhyamalar@yahoo.co.in

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 (1-2g/day), Paracetamol does not irritate stomach lining, kidney cells and liver cells. Studies reported that high dosage (>2g/day), resulted in Gastrointestinal complications, abnormal Kidney function, Liver damage.
[H.L. Vidhya Malar and S. Mary Mettilda Bai. **Beware Of Paracetamol Toxicity.** *Biomedicine and Nursing* 2015:1(3): 94-95]. ISSN 2379-8211 (print); ISSN 2379-8203 (online); http://www.nbmedicine.org. 11. doi:10.7537/marsbnj010315.11

Key words: 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. But paracetamol shows some strange and life threatening effects ie., 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. In1893, 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 discoverey 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.

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) (Hogestatt *et al., 2005)*. 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 (Kofalvi 2008). 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 (Ottani *et al* 2006).

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) (Borne & Ronald 1995). 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.

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 (>2g/day) does increase the risk of upper gastrointestinal complications (Rodriguez & Diaz 2000). 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 (Le & William 2004).

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 (Bower *et al* 2007). 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 (Colas Chacartegui *et al* 2005).

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 (Dart *et al* 2006).

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 (Larson *et al* 2005; Ryder & Beckingham 2001). 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.

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12/25/2015