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Original Research Paper

Toxicity and Mechanism of Action of Paracetamol

Medical Science

KEYWORDS :

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ABSTRACT

Aim: *To study the use of paracetamol and ibuprofen for pediatrics pain and fever.*

Study selection: *Data from original studies on pharmacogenomics, pharmacokinetics and pharmacology of paracetamol were included in the analysis.*

Results: *More published studies are required to comprehensively define the pharmacology and phamacokinetics of paracetamol and ibuprofen in paediatrics.*

Conclusion: *An understanding of drug metabolic processes during ontogeny may enable predictions about the capacity of children to cope with medications. Pharmacogenomic screening may help elucidate the inter-individual variation in drug metabolism and pharmacokinetics.*

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.

In general, paracetamol and ibuprofen are the most popular over-the-counter drugs used to manage fever and pain in children. Paracetamol and ibuprofen are effective antipyretics and analgesics (ibuprofen is favored in inflammatory conditions).1-4 Although these drugs are considered safe to use in recommended doses, a recent study has suggested a link between paracetamol and allergic disorders.5

Although some of the adverse effects of ibuprofen are well known, its indication and widespread use in paediatrics creates the potential for adverse reactions in children previously unexposed to ibuprofen. These concerns have raised questions about the empirical use of paracetamol and ibuprofen in children. In this article we will review the literature on the pharmacology and pharmacokinetics of paracetamol and ibuprofen pertaining to their use in paediatric pain and fever. Further, the inter-individual variation in hepatic enzymes which metabolise these drugs may account for some of the toxicity attributable to their use, as well as alack of efficacy in some cases.6

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 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 antiinflammatory 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).

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) [7]. Paracetamol is metabolized to AM404which 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 AM404inhibits sodium channels as like anesthetics, lidocaine and procaine [8]. 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 [9].

Paracetamol Metabolism

Paracetamol is metabolized in the liver via three pathways-glucuronidation, sulfation or via the hepatic cytochrome P450enzyme system, which is responsible for the toxic effects of Paracetamol due to alkylating metabolite N-acetyl-P-benzo-quinone imine (NAPQI) [10]. 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.

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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 [11]. Tirmenstein and Nelson, [12]and Tsokos-Kuhn et al. [13] reported alterations of plasma membrane ATPase activity following toxic doses of acetaminophen.

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 [14]. 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 [15].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 [16]. 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 [17].

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 [18].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 . 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 [19-20]. 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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