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Professional paper

TOXICITY AND THE MOST COMMON SIDE EFFECTS OF PARACETAMOL IN PEDIATRICS

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Abstract

Parcetamol is one of the most popular analgesic and antipyretic drugs. The existence of this drug in different pharmaceutical forms makes it even easier to use it at different ages. It is considered first-line treatment in children, for the treatment of pain and fever. With its widespread use, it has become one of the most common pharmaceuticals associated with accidental poisoning. Infants and children are particularly susceptible to acute overdose of paracetamol, which often causes: hepatotoxicity, hypothermia, thrombocytopenia, leukopenia, respiratory side effects, etc. In 80% of the presented cases, paracetamol was used for fever, therefore hypothermia is one of the most expressed symptoms. The main purpose of this study is to identify toxic doses of paracetamol in children, symptoms, management and treatment of these poisonings. From this research, in a single pediatric clinic, many paracetamol intoxications have occurred due to parents' mistakes, therefore these mistakes should be made known to the public in order to be avoided by others.

Keywords: Paracetamol, poisoning, dose, temperature, pain, hepatotoxicity, hypothermia, accidental poisoning.

1. Introduction

Paracetamol (international name used in Europe) and acetaminophen (international name used in the USA) are two official names of the same chemical compound derived from its chemical name N-acetyl para-aminophenol. This drug has a long history and, as is often the case with important discoveries, was discovered by accident (1). Since the 1980s, paracetamol has become the first drug of choice for the treatment of pain and fever in children in situations where the use of nonsteroidal anti-inflammatory drugs (NSAIDs) is contraindicated. After more than a century of discovery the use and some of the mechanisms of action, especially the effect on cyclooxygenase (COX) enzymes remain a matter of fierce debate. It is generally accepted that paracetamol has similar analgesic and antipyretic properties as NSAIDs, without anti-inflammatory activity. Otherwise, paracetamol is associated with fewer side effects than NSAIDs (2).

1.1. Mechanisms of Action of Paracetamol: Paracetamol in general is considered to be a weak inhibitor of prostaglandin (PGs) synthesis. Paracetamol is a weak inhibitor of COX-1 and COX-2 PG synthesis in damaged cell systems, but therapeutic concentrations of paracetamol inhibit PG synthesis in intact cells in vitro when substrate levels of arachidonic acid are low (less than about 5 mumol/L).
When arachidonic acid levels are low, PGs are synthesized by COX-2 in cells that contain both COX-1 and COX-2, that's why, the selectivity of paracetamol is related with the inhibition of COX-2-dependent pathways. COX-3, a splice variant of COX-1, has been suggested to be the site of action of paracetamol, but genomic and kinetic analysis indicate that this selective interaction is not clinically relevant. There are some evidence that the analgesic effect of paracetamol is central and is due to the activation of descending serotonergic pathways. The action of paracetamol at a molecular level is still unclear, but may be related to the production of reactive metabolites by the peroxidase function of COX-2 (3). Paracetamol has a stronger effect on COX preparations from the brain than on COX preparations from the spleen. It has been suggested that a third isoform of the enzyme, COX-3, may exist in the brain. Meanwhile, their action in inhibiting

central cyclooxygenase (COX)-3 is explained. The fact that acetaminophen acts functionally as a selective COX-2 inhibitor led us to consider the hypothesis that it worked through preferential blockade of COX-2. Many authors have confirmed through thromboxane B2-induced coagulation and Prostaglandin E2-induced lipopolysaccharide measured ex vivo and in vitro in human whole blood as COX-1 and COX-2 activity coefficients that acetaminophen inhibits COX-2 by more than 80%, i.e. to a similar degree to non-steroidal anti-inflammatory drugs (NSAIDs) and selective COX-2 inhibitors. The fact that acetaminophen acts functionally as a selective COX-2 inhibitor led us to examine the hypothesis that it worked through preferential COX-2 blockade (4).

1.2. Metabolism: Acetaminophen is extensively metabolized by the liver via three major hepatic pathways: glucuronidation, sulfation and oxidation of CYP450 2E1 (5). Approximately 90% of acetaminophen is conjugated to sulfated and glucuronidated metabolites that are eliminated by the kidneys (6). Of the remaining acetaminophen, approximately 2% is excreted unchanged in the urine, and the remainder undergoes CYP450-mediated oxidation to form a reactive metabolite, N-acetyl-p-benzoquinone imine (NAPQI) (7). Under normal circumstances, this toxic metabolite reacts with sulfhydryl groups on glutathione, converting it to harmless metabolites before being excreted in the urine (Figure 2) (8).

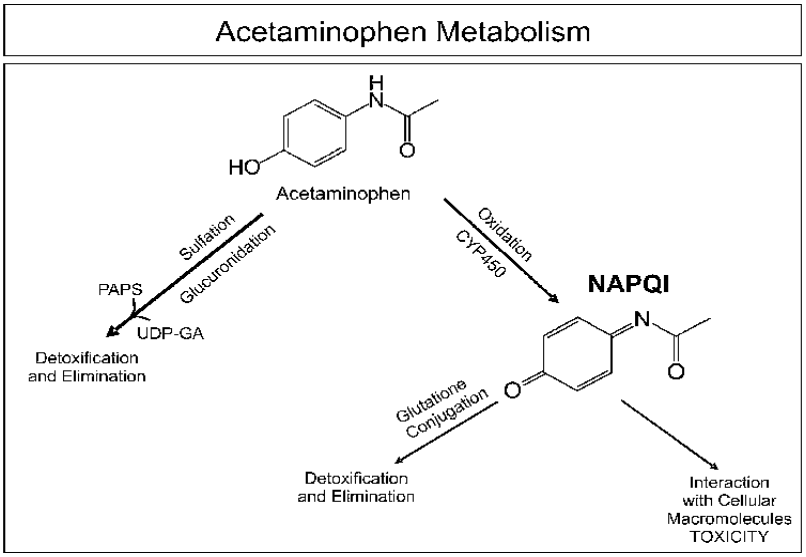

Figure 2: Metabolism of paracetamol. Paracetamol mainly undergoes metabolism through sulfation and glucuronidation. Formation of NAPQI (N-acetyl-p-benzoquinone imine) results via oxidation by CYP, leading to toxicity, or detoxification via GSH (glutamyl-cysteinyl-glycine) conjugation (Moyer, 2011)

1.3. Toxicity and The Most Common Side Effects: In general, paracetamol is well tolerated when administered in therapeutic doses. Incidentally, there may also be a rash or allergic reaction. The rash is usually in the form of erythema or urticaria, but is sometimes more serious and may be accompanied by fever and mucosal lesions. The use of paracetamol is reportedly associated with neutropenia, thrombocytopenia and pancytopenia. The most serious side effect of paracetamol overdose is hepatic necrosis with fatal potential. Overdose can also cause renal tubular necrosis and hypoglycemic coma. The mechanism by which paracetamol overdoses leads to hepatic cell damage and death involves its conversion to the toxic metabolite NAPQI. The glucuronide and sulfate linkage pathways become diluted and increased amounts lead to the process of NAPQI formation through N-hydroxylation by the CYP mediator.
This is immediately eliminated by binding to GSH and subsequent metabolism to mercapturic acid and excreted in the urine. In this paracetamol overdose, the GSH levels in the liver cells are depleted. The potent metabolite NAPQI binds covalently to cellular macromolecules, leading to dysfunction of enzymatic

systems and structural and metabolic derangement. Further, cellular depletion of GSH renders hepatocytes highly susceptible to oxidative stress and apoptosis (9).

1.4. Pharmacological Differences Between Children and Adults: Some basic pharmacological effects differ between children and adults. Furthermore, there are differences between different pediatric age groups. The greatest differences exist between newborns and adults. The absorption of the drug depends on the way of assimilation and the biochemical characteristics of the drug. Most drugs in pediatrics are administered orally and therefore gastric pH and gastrointestinal motility are important. Absorption of the drug does not appear to differ significantly between infants, older children, or adults. The metabolism of a drug is often dependent on the liver. The rate of metabolism depends on two factors: the size of the liver and the effectiveness of the enzymes. Children have a much larger liver size relative to their body weight than adults; Liver volume relative to body weight is twice as high in a 1-year-old child as in a 14-year-old child. Then, children have a higher metabolic rate than teenagers and adults. An exception is newborns as their enzyme production capacity is still immature and cannot yet function effectively. Renal elimination is an important way of drug elimination. Tubular secretion and re-absorption are immature at birth, but they reach maturity during the first year of life and reach adult capacities (10).

1.5. Paracetamol Intoxication in Children: Three main routes of ingestion lead to paracetamol intoxication in children; intentional overdose, inadvertent exposure or administration error. Because of its popularity in pediatrics, children are often given this drug. Paracetamol for adults and children are often stored at home and may be readily available to children, risking the possibility of accidental poisoning in children by ingesting the drug. The acute toxic dose for children appears to be more than 200 mg/kg body weight. In case of repeated doses, intoxication seems to occur after application of more than 75 mg/kg body weight per day in children younger than 6 years. The acute toxic dose in adolescents is considered to be more than 7.5 g in a single dose. However, children appear to be less susceptible to acute poisoning than adults. One hypothesis to explain the lower rate of severe intoxication in children compared to adults refers to their larger liver size relative to body weight. Next, children are probably able to metabolize paracetamol more effectively than adults because of their greater glutathione stores. The real incidence of liver failure in pediatric patients due to paracetamol intoxication remains unclear. The US and UK report that paracetamol intoxication is the leading cause of pediatric liver failure, accounting for 14% of all cases. Most of these poisonings are due to intentional overdose in adolescents, but there appears to be a global increase in accidental overdose in children (10).Therapeutic doses of acetaminophen can dramatically cause hypothermia in febrile children. Physicians should be aware of this possible, very rare, side effect in children receiving acetaminophen, especially after vaccination, where hypothermia may be mistakenly attributed to the vaccine when it is secondary to acetaminophen. During the occurrence of hypothermia in small children from paracetamol, as a permanent side effect, most of them do not dare to use paracetamol throughout their lives (11). For a very common type of poisoning, evidence on how to treat patients with paracetamol poisoning is surprisingly weak. Furthermore, most of the available evidence is derived from research conducted in adult patients.

In young children, the primary risk assessment that is determining the actual dose or doses and timing of dosing is difficult. This difficulty greatly affects treatment decisions. However, the mainstay of treatment is the use of the antidote N-acetylcysteine when plasma levels exceed toxic levels. In remote areas, oral methionine can only be given when N-acetylcysteine is not available (12). Children who receive appropriate treatment generally have a good prognosis, especially when treatment is started within 8 hours of acute paracetamol ingestion, with up to 10% hepatotoxicity. Based on observational data from the Pediatric Acute Liver Failure Study Group, recovery occurred in 94% of paracetamol overdose cases in children when treated appropriately. Initial management consists on providing general supportive care of the airway,

breathing and circulation, as well as the administration of activated charcoal (1 g/kg – maximum dose 50 g) in patients who present for care within four hours of receiving a dose of unknown potentially toxic effects of paracetamol. Patients presenting for care after four hours are unlikely to benefit from activated charcoal unless agents that slow gastric motility (opioids, calcium channel blockers, anticholinergic agents) have also been ingested (13).

The primary goal of this study is to prevent the excessive use and high doses of paracetamol through the knowledge of pharmacists on the toxicity of paracetamol and its treatment, as well as to increase the awareness of parents in order to reduce cases of intoxication in Tetovo and wider, R. of North Macedonia. The specific objectives are;

- Detection of the age group and gender of patients who have been on paracetamol therapy.
- Indications for the use of paracetamol.
- Symptoms, management and treatment of these poisonings.

2. Material and Methods

This research was carried out from the data collected from the patients' histories, from the private clinic "AR Medika" in Tetovo, with the consent and permission of the parents and the director of the clinic. Patients were informed in advance about the purpose of the study, about privacy and anonymity (14). In this research, we followed a larger number of patients who used paracetamol for cold, fever or pain, but we presented only 15 cases of children who showed symptoms of toxicity.

Patients are divided into 2 age groups:

- First age group (I): Children under the age of 1 year - up to 1 year.
- Second age group (II): Children aged 2-5 years.

2.1. Statistical data processing: The results were processed and presented in tabular and graphical form using Microsoft Office Excel 2007.

3. Results and Discussion

3.1. Age of Patients: The age of the patients in the presented cases includes children under the age of 1 year to the age of 5 years. Of the cases included in the study, 5 cases include the first age group (33%) and 10 cases include the second age group (67%), which are presented in "Figure 1".

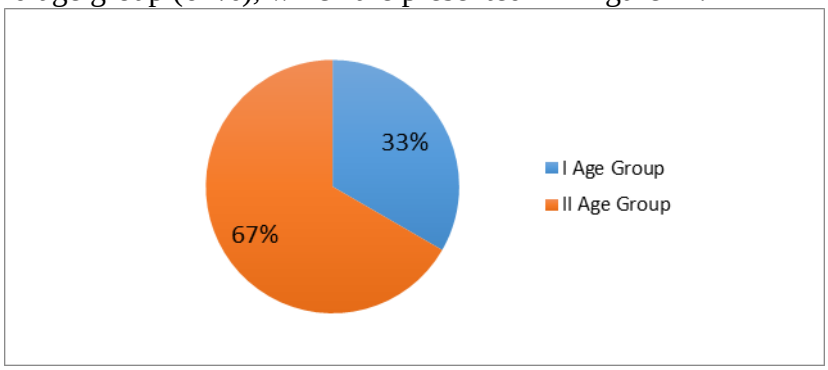

Figure 1. Age group of patients divided into percentage

3.2. Gender of patients: Of all the cases collected, 8 patients are female (53%), and 7 patients are male (47%), which are shown in "Figure 2".

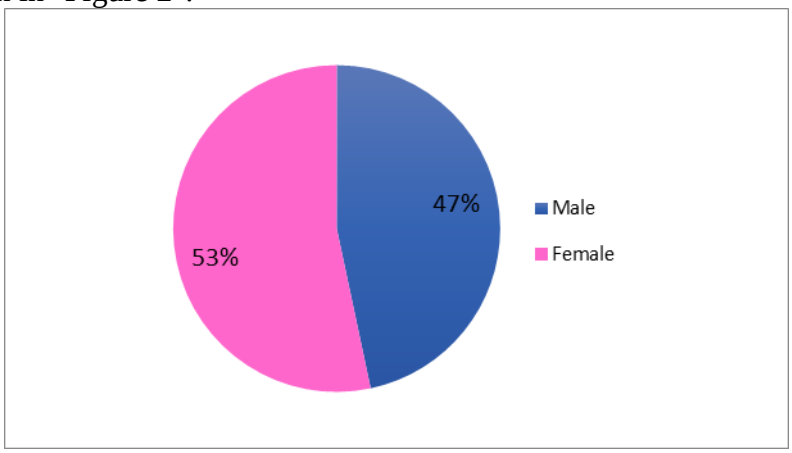

Figure 2. The gender of patients divided into percentage

3.3. Indications for the use of paracetamol: From the investigated cases, the drug was used to reduce temperature (80%), for cold symptoms (13%) and for pain (7%), as shown in "Figure 3".

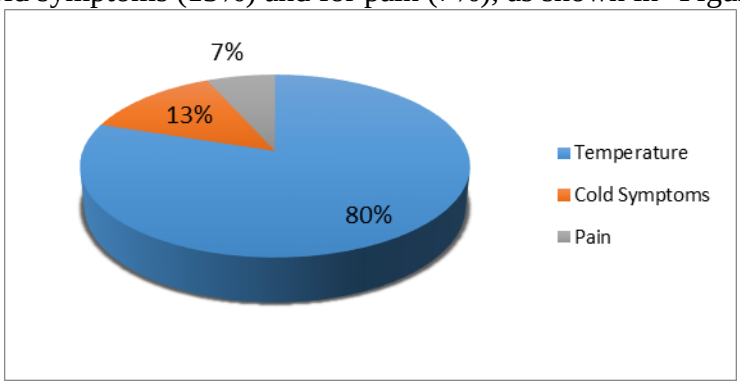

Figure 3. Paracetamol use indications

It has been proven that in 80% of cases, intoxications are the result of overdose and carelessness of the parents, where the parents themselves give their children paracetamol syrup in a dose of 250 mg at repeated intervals for a short time. In 20% of other cases, the toxicity has come as a result of the abuse of other preparations (paracetamol in combination with other analgesics) for a faster treatment or without knowledge about the doses of paracetamol that these products contain.

3.4. Symptoms: In patients from 0-1 years old, after overdose with paracetamol, the temperature drops below 35 °C, hypothermia, apathy, drowsiness appear, the patient sleeps for a long time, they have a decrease in appetite, etc. Patients aged 1 year, after the appearance of hypothermia, do not dare to use paracetamol again, since even small doses can lead to hypothermia again. There are cases of patients who, after hypothermia in childhood, do not dare to use paracetamol even in old age. In patients over 1 year of age after overdose with paracetamol, signs of hypothermia, leukopenia and thrombocytopenia appeared up to 7 days after stopping paracetamol "Figure 4". Patients over 1 year old, whose temperature has dropped to 35 °C, have been treated with combined therapy with Vitamin C, Vitamin therapy.

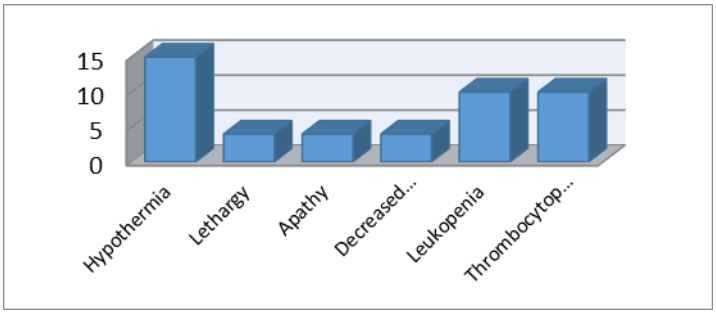

Figure 4. Symptoms presented during poisoning

4. Discussion

In this study, the toxicity of paracetamol, as an OTC-preparation widely used in pediatrics, was presented. In all cases analyzed, it turned out that one of the most pronounced symptoms of toxicity was hypothermia. Our results correspond to the data of A.P. M.-S. Agier, et al (15), where 9 pediatric patients developed hypothermia after paracetamol overdose, these cases were identified from the French Pharmacovigilance Database (FPVD), which includes all adverse drug reactions (ADRs) reported to the 31 French Regional Pharmacovigilance Centers since 1985.

5. Conclusion

Paracetamol poisoning is very common in children. Although serious complications are rare, they can have consequences that lead to acute liver damage. When adequately treated with specific acetylcysteine antidotes as well as discontinuation of therapy, paracetamol toxicity can be reduced to a minimum without serious side effects. It is very important for a clinician to have a good insight into the pathophysiology of paracetamol-induced toxic liver failure and the mechanisms of action of acetylcysteine so that he can provide optimal evidence-based treatment in order to prevent fatal injuries. First, the public believes that it is a safe drug, second, it is easily available in the market, unintentional misuse is the third leading reason for poisoning children. Finally, dosing errors can occur due to errors by parents, doctors and even pharmacists. Strategies to prevent fatal overdoses should target patient- and systems-based interventions. In North Macedonia, cases of paracetamol poisoning are quite rare, therefore this study was carried out to draw the attention of the population, especially parents, to the risks associated with the toxicity of paracetamol during the administration of high doses, or even during the administration in therapeutic doses at more frequent time intervals, because they can be fatal.

"Do we know everything about paracetamol?" - the coming years will undoubtedly give the answer if the decision made in 1956 to introduce paracetamol as an OTC drug was correct.

Nomenclature

COX-1 Cyclooxygenase1
COX-2 Cyclooxygenase 2
COX-3 Cyclooxygenase3
CYP450Cytochrome P450
NAPQI-N-acetyl-p-benzoquinone imine
GSH-Glutathione-cysteine-glycine

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