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Intentional and accidental paracetamol poisoning in childhood – a retrospective analysis

Celowe i przypadkowe zatrucia paracetamolem wśród dzieci – analiza retrospektywna

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Introduction: Paracetamol is one of the most commonly used *analgesics* and *antipyretics* available without limits as preparations of the OTC group (over the counter drugs). Overdose and poisoning with this drug always brings about the risk of acute hepatic failure. The objective of the study was a retrospective evaluation of patients hospitalized in the Paediatric Clinic during the period 2004–2012 due to poisoning with paracetamol.

Material and methods: The analysis covered 44 patients hospitalized in the Paediatric Clinic during 2004–2012 due to poisoning with paracetamol. Patients were divided into three groups: intentional poisonings, accidental poisonings, and drug overdose.

Results: During the period of the study, 44 patients aged 2.1–17.1, poisoned with paracetamol, were hospitalized. Among these patients there were 30 (68.2%) cases of intentional poisonings, 10 (22.7%) of accidental poisonings, and only 4 patients (9.1%) were children hospitalized after a paracetamol overdose. The majority of patients in all groups were females (93.3%).

Discussion: Paracetamol intoxication may occur after exceeding a single allowable dose, in the case of intentional poisoning, more rarely after exceeding the daily dose, in the case of intense pain complaints, or in the treatment of persistent fever.

Based on the analysis performed, an increase was observed in the frequency of poisoning with paracetamol, especially intentional poisoning. Unlimited access to paracetamol as an OTC drug should be reconsidered.

Key words: paracetamol poisoning • OTC drugs • children

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List of abbreviations: **CNS** – central nervous system, **COX** – cyclooxygenase, **INR** – international normalized ratio, **MARS** – molecular adsorbents recirculating system, **NAC** – N-acetylcysteine, **OTC** – over-the-counter drugs.

Introduction

Among all pharmaceuticals available, the over-the-counter (OTC) drugs are available basically without limits, and not only in pharmacies. Basically, OTC drugs should be safer and much weaker than those dispensed on prescription by a doctor. This group of medicinal products includes, among others, paracetamol (in Europe), and acetaminophen (in the United States) – a drug commonly applied as an *analgesic* and *antipyretic* [5,7,14]. At present in Poland, it is among the drugs most frequently sold over the counter.

The mechanism of paracetamol action, similar to other non-steroid anti-inflammatory drugs, consists in inhibition of the synthesis of prostaglandins through the inhibitory effect on cyclooxygenase (COX) – the key enzyme participating in the conversion of arachidonic acid to prostaglandin H_2. Within COX, three isoenzymes are distinguished: COX-1 (constitutive form), COX-2 (inducible form), and COX-3 (present in the CNS). Paracetamol is the preferential isoenzyme COX-2 inhibitor, and a selective inhibitor of COX-3 isoenzyme [1]. Due to the lack of considerable inhibition of the synthesis of prostaglandins outside the CNS, paracetamol does not cause many side effects which accompany other non-steroid anti-inflammatory drugs.

It is known that during the period of adolescence an increase is noted in the frequency of intentional poisonings, including those for suicidal purposes. Patients often reach for drugs available at home in the medicine cupboard, and often when planning a suicide attempt to take widely available pharmaceuticals, including the OTC, which may be bought anywhere, without limits and in any amount. On the market, there is a tremendous amount of preparations containing paracetamol, which are available over the counter and create a great risk of overdose. The objective of the study was to perform a retrospective analysis of patients hospitalized in the Paediatric Clinic during 2004–2012 due to paracetamol poisoning. Attention was attracted to the threats associated with easy access to paracetamol, by the analysis of the frequency and incidence of poisoning with this preparation.

Material and methods

In the retrospective study, an analysis was performed of patients hospitalized in the Paediatric Clinic at the Children's Clinical Hospital in Lublin in 2004–2012 due to paracetamol poisoning. Based on medical records, the circumstances of consumption of this drug were assessed, which allowed the selection of three groups of patients: those treated due to intentional poisoning, accidental poisoning, or as the result of acetaminophen overdose. The amount of the preparation taken was analysed by calculating the amount of the substance consumed per kilogram of body weight. The time that had elapsed from the moment of intoxication until hospitalization was calculated, simultaneously paying attention to the clinical symptoms of poisoning and the concentration of paracetamol in the blood.

Results

Based on the retrospective analysis of medical records, it was found that during the period 2004–2012, 44 patients poisoned with paracetamol were hospitalized in the Paediatric Clinic at the Children's Clinical Hospital.

During the period of the study, an upward tendency was observed in the incidence of poisoning with acetaminophen, especially among girls (Fig.1).

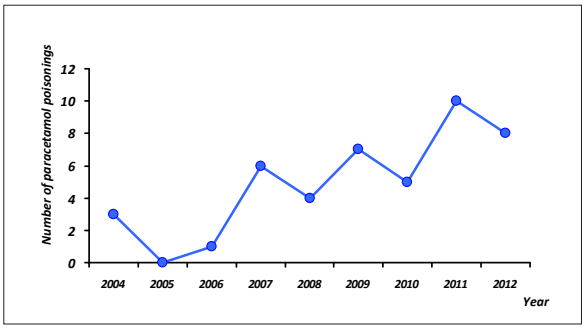

Fig. 1. Number of patients hospitalized in the Paediatric Clinic due to paracetamol poisoning during 2004-2012

The majority of patients in this group – as many as 68.2% (30 cases) – were patients who had undertaken a suicide attempt, followed by 22.7% (10 cases) of patients with accidental poisoning, and only 9.1% (4 cases) were children who overdosed with the drug taken for intense pain (Fig. 2).

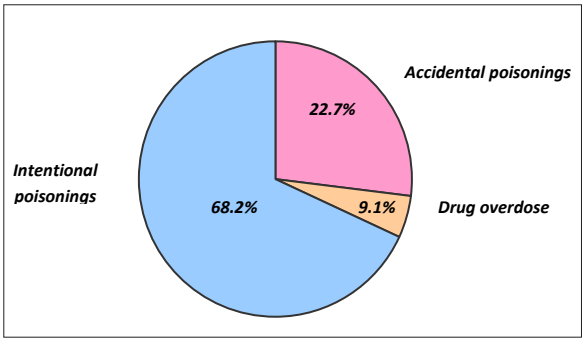

Fig. 2. Percentage distribution of the causes of paracetamol poisonings in patients hospitalized in the Paediatric Clinic during 2004-2012

The age of patients hospitalized due to poisoning varied according to the type of intoxication. Patients treated after intentional poisoning with paracetamol were adolescents aged from 12 to 17.1; mean age 14.8. Small children aged 2.1–5.8 were typically victims of accidental poisoning; mean age of these patients was 3 years. Drug overdose concerned older children aged 13.3-16.1; mean age 14.8.

Among the total number of patients hospitalized due to intoxication with paracetamol, females dominated – 37 patients (84%). Figure 3 presents the distribution of patients treated due to paracetamol poisoning according to gender in individual years.

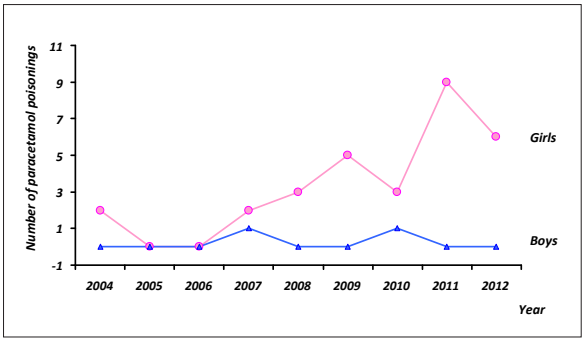

Fig. 3. Number of patients hospitalized in the Paediatric Clinic due to paracetamol poisoning during 2004-2012 according to gender

Female gender dominated among patients who received treatment after a suicide attempt – among 30 patients as many as 28 were girls (93.3%). Also, all the patients hospitalized after paracetamol overdose were females. Among patients treated due to accidental poisoning with acetaminophen, the distribution by gender was similar – among 10 patients, 6 were girls (60%).

The greatest amount of the drug consumed calculated per kg of body weight was noted among patients hospitalized due to intentional poisoning – from 56 to 490 mg/kg, on average 192 mg/kg body weight, i.e. above the toxic dose. In this group, 5 children (11%) with the features of hepatic failure were referred to a centre with a higher referential level, i.e. to the *Clinic* of *Gastroenterology, Hepatology* and *Nutrition at the* Memorial *Child Health Centre* in Warsaw. Among patients who received treatment for accidental poisoning, the amount of drug consumed was 115 mg/kg of body weight, on average (from 50 to 213 mg/kg of body weight). In the case of drug overdose, the amount of paracetamol consumed was low: 24 mg/kg of body weight on average (21–28 mg/kg of body weight). All patients in this group were discharged home in a good condition, without features of liver impairment.

Table 1 presents data concerning patients hospitalized due to paracetamol poisoning during the period of the study.

In all patients admitted to hospital after the consumption of an excessive dose of paracetamol, gastric lavage was performed, and activated charcoal administered. In each patient, blood was collected for determination of the level of paracetamol, and risk of occurrence of acute hepatic failure evaluated using the Rumack-Matthew nomogram. Hepatic function was monitored by evaluation of liver enzymes' activity, concentration of the total and bound, and the INR value.

Table 1. Data concerning patients after paracetamol poisoning

	Mean age of patient (yrs)	Amount of paracetamol consumed in mg/kg of b.m	Patients at risk of occurrence of acute hepatic failure
Intentional poisoning	15 (12-17)	192 (56-490)	5 (11%)
Accidental poisoning	3 (2-4)	115 (50-213)	0
Drug overdose	15 (14-16)	24 (21-28)	0

All the patients admitted to hospital after the consumption of an excessive dose of paracetamol or medications containing paracetamol, irrespective of the clinical symptoms, the time that had elapsed from intoxication to hospitalization, after collecting blood for laboratory tests for hepatic function and level of paracetamol, were treated with intravenous Nacetylcysteine (NAC) infusion, according to the official scheme. In 15 cases (34%), the therapy was terminated after obtaining a very low, safe level of paracetamol in blood plasma.

Discussion

Paracetamol is one of the most commonly used *analgesics* and *antipyretics*, available without limits not only in pharmacies, but also at petrol stations and shops. This drug is considered as safe, which is confirmed by many advertisements on the television and radio and in the press [4,5,7,11,14]. It is known that the mechanism of the action of paracetamol consists in the inhibition of synthesis of prostaglandins through the inhibitory effect on cyclooxygenase (COX) – the key enzyme participating in the conversion of arachidonic acid to prostaglandin H_2. Paracetamol is a preferential inhibitor of COX-2 isoenzyme and a selective inhibitor of COX-3 isoenzyme [1]. Due to the lack of considerable inhibition of the synthesis of prostaglandins outside the central nervous system (CNS), paracetamol does not cause many side effects which accompany other non-steroid anti-inflammatory drugs.

Intoxication may occur after exceeding a single allowable dose (in the case of intentional poisoning), more rarely after exceeding the daily dose, in the case of intense pain complaints, or in the treatment of persistent fever [3,5,8,10,14].

The pharmacokinetics of this drug is well known; bioavailability depends on dose, route of administration, and the meal consumed. Generally, after several minutes, over 90%

of the drug consumed penetrates into the blood, the analgesic effect occurs 15–30 minutes after oral administration, maximum concentration is reached after 10–60 minutes, half-life is from 2 to 4 hours, and the effect lasts for 4–6 hours. As much as 95% of paracetamol is metabolized in the liver [5,6,7,11,14].

Acetaminophen applied in therapeutic doses is considered a safe drug. Opposite to non-steroid anti-inflammatory drugs, it is recommended to patients with asthma, peptic ulcer, and blood clotting problems [14]. The most dangerous consequence of overdose, of which young people who are subject to intentional poisoning are unaware, is toxic liver lesion. This results from the hazardous effect of paracetamol metabolite synthesized via cytochrome P450, and the exhaustion of body reserves of glutathione (used in the metabolism of acetaminophen). The consequence of this is the disorder in paracetamol conjugation via cysteine and mercapturic acid [5,14].

The frequency of poisoning with acetaminophen remains constantly at a high level, especially among adolescents [5,7,8,9,10,14]. The presented retrospective study confirms an increase in the frequency of paracetamol intoxication within the last two years. Similar observations have also been made by other researchers [8]. However, the data obtained in the present study cannot serve as complete statistics of paracetamol poisonings in the Lublin macroregion. This is because there is a lack of specialist paediatric toxicology wards, and it cannot be excluded that children with a similar problem are also hospitalized in other regular paediatric wards.

In every society, suicide attempts constantly remain a great problem of a social and psychological nature. It is observed that among patients hospitalized due to intoxication with paracetamol there dominate those treated due to intentional poisoning with this drug [8,10]. Based on the results of the analysis performed, it was confirmed that among the total number of patients hospitalized after intoxication with paracetamol, as many as 68.2%, i.e. 30 patients, received treatment due to intentional poisoning.

Similarly, a high incidence of intentional poisoning was confirmed in the study by Meyers et al. [8] (85%), and by Schmidt (89% of intentional poisonings in the age group up to 40) [10]; also in the study by Craig et al., 75.4% of paracetamol poisonings were suicide attempts [2].

In the Paediatric Clinic at the Children's Clinical Hospital, during the period of study, 37 female patients who were poisoned with paracetamol were hospitalized, which constituted 84%. This is in accordance with the data from the literature. In the study by Myers et al., 68% of patients hospitalized due to paracetamol poisoning were females [8]. Schmidt, in his retrospective evaluation of patients treated for intoxication with paracetamol in Denmark, confirmed the domination of girls (as many as 63%) [10]. In the study by Craig et al., the percentage of females was close to that of males (52.5%) [3], while in the study by Yip et al. the percentage of patients poisoned with paracetamol was even higher (85%) [13]. Also, Waring et al. reported that the percentage of females poisoned with paracetamol was higher than that of males (68.1%) [12].

Paracetamol poisoning is among the most frequent causes of acute hepatic failure, not only in Poland, but also in the United Kingdom and the USA [2,3,4,10].

Acute hepatic failure following intoxication with paracetamol occurs after consumption of over 150 mg/kg of body weight. The prognosis depends not only on the dose taken, but also on the level of paracetamol in the blood, application of adequate treatment in the proper time, use of other drugs, especially those inducing cytochrome P450, or exhausting glutathione reserves. The risk of paracetamol toxicity is evaluated using the Rumack-Matthew nomogram, where the axis of ordinates is the time elapsed from the consumption of the drug in hours, and the axis of abscissae is the level of paracetamol in blood plasma. The graph presents the possible risk of liver lesion, based on the concentration of acetaminophen in blood plasma, with consideration of the time that has elapsed from the consumption of the toxic dose [12,13,14] (Figure 1).

On assumption, patients with borderline and higher levels of paracetamol according to the Rumack-Matthew nomogram should be treated in any case. Considering difficulties with the specification of the time between consumption of the drug and the moment of its determination, attention is paid to the activity of aminotransferases, as well as the value of the prothrombin ratio (INR) within the first 48 hours after the probable consumption of the drug [10,13,14].

Within the first hours after the consumption of the toxic dose, gastric lavage and administration of activated charcoal are recommended, in order to prevent further absorption of the drug. An important antidote applied in paracetamol poisoning is N-acetylcysteine (NAC), a precursor of glutathione. The treatment starts immediately after the suspicion of the intake of a toxic dose of the drug, not waiting for the result of the level of paracetamol in blood plasma [2,3,4,5,6,9,10,11,12,13,14].

Such a procedure was applied in all patients in the present retrospective study, irrespective of the reported dose of the drug consumed, assumed time between consumption and hospitalization, and clinical symptoms observed. In 15 cases, the therapy was discontinued after obtaining a low, safe result of paracetamol level in blood plasma, especially with a good general wellbeing and normal markers of hepatic function.

Literature reports emphasize the relationship between high activity of aminotransferases, elevated level of bilirubin, an increase in the INR, and the dose of paracetamol consumed [14]. A single elevation in INR with normal activities of aminotransferases is associated with inhibition by paracetamol of the activation of vitamin K-dependent factors, rather than the toxic effect of the drug on the liver [5].

It may be assumed that the higher the dose of paracetamol taken per kilogram of body weight, or the longer the time between consumption of the drug and application of the antidote, the higher the risk of liver lesions. It should be added that this risk increases with the consumption of, e.g. complex preparations containing paracetamol and opioids, slowing down peristalsis and prolonging paracetamol absorption. Also, the consumption of alcohol is conducive to hepatotoxicity of paracetamol through the decrease in glutathione reserves [2,3,10,13,14].

In the group of patients evaluated in the present study, in 5 (11%) children increasing activity of aminotransferases was found, together with elevated values of bilirubin and INR. In the remaining patients, no features of hepatic lesions were observed. Laboratory tests evaluating hepatic function did not significantly differ from normal.

The risk of toxic liver lesion always exists. We are never certain how high a dose the patient consumed, whether he/she did this once or repeated the intake of a toxic dose, and during what period of time. We also often do not know about other drugs or toxic agents which the patient may have consumed, and which may affect the pharmacokinetics, metabolism and undesirable effects of acetaminophen. In the case of patients who have an unfavourable prognosis, the treatment should be continued in centres where liver transplantation is possible, where there is the possibility to perform albumin dialysis of the MARS type (molecular adsorbents recirculating system). This is a procedure that supports the liver detoxification function, also called 'liver dialysis', usually applied in patients in whom it is planned to perform liver transplantation [5]. As mentioned above, in the Paediatric Clinic, among 44 children hospitalized after paracetamol poisoning, 5 (11%) were referred to a centre with a higher degree of reference due to acute hepatic failure, with high activities of aminotransferases and elevated INR. In the report by Schmidt, 17% of the total number of patients poisoned with paracetamol developed acute hepatic failure.

Suicide attempts among adolescents are often of a manifestation character, a wish to attract attention to oneself, and are rarely the manifestation of deep depression. Each child intentionally poisoned with paracetamol was examined by a clinical psychologist, and, in the cases of suspicion of personality disorders or pathological states related to depression, examined by a psychiatrist or referred to a specialist ward for detailed diagnosis.

Considering the frequency of intentional poisoning among children, despite the low percentage of a severe complication in the form of acute hepatic failure, it is justifiable to consider the safety of unlimited access to this drug.

Conclusions

1. Within recent years, a constant increase in the frequency of poisoning with paracetamol, especially intentional poisoning, has been observed.

2. Poisoning with paracetamol is always associated with the risk of acute hepatic failure.

3. The unlimited availability of paracetamol as an OTC drug should be reconsidered.

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