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Unintentional overdose of paracetamol as a problem of modern times - a case report

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ABSTRACT

INTRODUCTION

Paracetamol is one of the most widely used analgesics and antipyretics in the world. An overdose of this drug can occur after a single ingestion of a large amount of paracetamol or after repeated ingestion of smaller amounts that eventually exceed the recommended total dose and can result in liver damage. It is believed that the maximum daily dose of paracetamol for an adult is 4g.

MATERIALS AND METHOD

Patient information was collected from hospital records available in the clinical toxicology department. In addition, we conducted a literature review on paracetamol using PubMed.

CASE REPORT

A patient, 16 years old, was admitted from a district hospital to the Clinical Toxicology and Cardiology Department in Lublin for paracetamol intoxication and suspected intoxication with a psychoactive substance. The patient's history revealed that he had taken a total of 20 paracetamol 500mg (10g) tablets in short intervals of 2 h for abdominal pain. The patient was treated with a full dose of antidote (ACC), and the drug infusion was continued at a maintenance dose. Despite the treatment administered, increasing features of liver damage were observed (INR 2.78, AST 6273 U/l, ALT 8854 U/l, bilirubin 3.83 mg/dl).The patient was consulted to qualify for a possible liver transplant. With intensive treatment maintained, a downward trend in liver damage parameters was achieved. The patient was discharged from the Department in good general condition, without complaints.

CONCLUSION

Due to the increasing number of paracetamol overdoses (intentional or accidental), strategies should be implemented to raise awareness and prevent this-educating patients, encouraging label/leaflet reading, reducing the amount of paracetamol in packages, more visible warnings on packages.

KEYWORDS: paracetamol; acetaminophen; paracetamol overdose; acetaminophen overdose

INTRODUCTION

Paracetamol (acetaminophen, APAP) is one of the most widely used analgesics and antipyretics in the world (it has no anti-inflammatory effect). [1, 2] This drug has analgesic effects in headaches, sore throat, migraines, toothaches, bone, joint and muscle pain, and painful menstruation. In addition, it can be used for colds and flu-like conditions. [3] It is commonly used as a first-line symptomatic drug for the treatment of fever and pain in the pediatric population and is the only drug recommended for the treatment of fever in newborns. [4] Paracetamol is said to be used from cradle to grave. [5] It is used at all three stages of the WHO pain relief ladder, and is the drug of choice in patients in whom administration of non-steroidal anti-inflammatory drugs is contraindicated, such as in cases of gastric ulcer disease, hypersensitivity to aspirin, impaired blood clotting, pregnant women, nursing mothers, and children with elevated body temperature associated with illness (illness-related fever). [5, 6] Due to its low cost and easy accessibility, it is an ingredient in many over-the-counter (OTC) and prescription medications worldwide, either alone or in combination formulations. [6, 7]

Paracetamol was originally synthesized in 1878 by Morse and first used clinically by von Mering in 1887. It was approved for clinical use in the 1950s, but it wasn't until the 1970s that concerns about its safety began to be raised. [8]

Paracetamol has a well-established safety profile when the recommended doses are used, and shows minimal interactions with other drugs. [5, 9] The action is similar to that of non-steroidal anti-inflammatory drugs (NSAIDs)(it is on average a weaker analgesic than NSAIDs), and is particularly similar to selective cyclooxygenase type 2 (COX-2) inhibitors. Despite its similarity to NSAIDs, the mode of action of paracetamol has been uncertain, but it is now widely accepted that it inhibits COX-1 and COX-2 through metabolism by the peroxidase function of these isoenzymes. [5, 6] Paracetamol administered orally is mainly absorbed in the small intestine. [2] The rate of absorption decreases when paracetamol is taken with a meal. [3] Thirty to sixty minutes after ingestion, acetaminophen reaches peak concentration with a half-life to 4 hours. [3, 7] The therapeutic serum concentration of paracetamol is less than 20 μg/ml (130 μmol/L). [2] After therapeutic doses, paracetamol is eliminated mainly by glucuronidation and sulfation (actually sulfonation), which account for about 55% and 30% of total urinary excretion of paracetamol, respectively. [10] Approximately 5-10% of the drug is oxidized by CYP450-dependent pathways (mainly CYP2E1 and CYP3A4) to a toxic electrophilic metabolite, imine N-acetyl-p-benzoquinone (NAPQI). [11] Although NAPQI is highly reactive, it is rarely harmful after ingestion of

therapeutic doses because it is rapidly conjugated with abundant glutathione stores in the liver and excreted through the bile. [1] When high doses of paracetamol are used, hepatic glutathione stores may be depleted, resulting in the accumulation of a toxic metabolite in the liver. [3] NAPQI, which is not detoxified, can bind to hepatocytes and cause cell necrosis [11].

Table 1 (Tab. 1.) shows the therapeutic doses of paracetamol for humans. [2]

Table number 1 (Tab. 1.) Therapeutic doses of paracetamol.

THERAPEUTIC DOSES OF PARACETAMOL		
ADULTS	Oral	650 - 1000 mg every 4 - 6 h, up to 4 g/day
	Intravenously, at a weight > 50 kg	650 - 1000 mg every 4 - 6 h, up to 4 g/day
	Intravenously, at a weight < 50 kg	12.5 to 15 mg/kg every 4 - 6 h, up to a dose of 3750 mg/day = 75 mg/kg/day
CHILDREN	Oral	10 - 15 mg/kg every 4 h, up to 60 mg/kg/day
	Intravenously	12.5 - 15 mg/kg/day every 4 to 6 h, up to 75 mg/kg/day

It is believed that the maximum daily dose of paracetamol for an adult is 4g. [6] However, due to the increasing number of overdoses in 2012, the FDA suggested, but did not mandate, that the maximum daily dose for adults should be 3g. [7]

Table number 2 (Tab. 2.) lists the one-time toxic doses for humans and the toxic doses in situations of repeated administration of so-called Repeated Supratherapeutic Ingestion (RSI). [2]

Table number 2 (Tab. 2.) The one-time toxic doses for humans and the toxic doses in situations of repeated administration of so-called Repeated Supratherapeutic Ingestion (RSI).

A SINGLE DOSE TOXIC TO HUMANS	
Adults	> 150 mg/kg or >7,5 g
Children	> 200 mg/kg or 10 g
TOXIC DOSE IN A SITUATION OF REPEATED ADMINISTRATION OF SO-CALLED SUPRATHERAPEUTIC INGESTION (RSI - REPEATED SUPRATHERAPEUTIC INGESTION)	
Patients under 6 years of age	> 200 mg/kg paracetamol in one day
	> 150 mg/kg per day for 48 h
	> 100 mg/kg per day for 72 h or longer
Patients over 6 years of age	At weight > 50 kg: > 4 g/day
	At weight < 50 kg: > 75 mg/kg/day

The excellent tolerability, especially gastrointestinal tolerance of therapeutic doses of paracetamol and better side effect profile than other analgesics, is the main reason for paracetamol's recommendation and wide acceptance as an analgesic. [5] Table 3 (Tab. 3.) lists the side effects of paracetamol. [3, 6, 8, 11, 12]

Table number 3 (Tab. 3.) Side effects of paracetamol.

SIDE EFFECTS OF PARACETAMOL
acute liver failure (ALF), central hepatic necrosis, renal tubular necrosis and hypoglycemic coma in overdose; may potentially increase blood pressure and promote blood clots; thrombocytopenia; anaphylactic reactions; skin hypersensitivity reactions including skin rash, angioedema and severe skin reactions such as: acute generalized pustular dermatitis, bullous erythema multiforme, (Stevens-Johnson syndrome) and toxic epidermal necrolysis (Lyell's syndrome); bronchospasm in patients with hypersensitivity to acetylsalicylic acid and other nonsteroidal anti-inflammatory drugs; paracetamol interferes with the production of prostaglandins. This may aggravate the development of intestinal ulcers, renal dysfunction and hypertension; paracetamol use has also been linked to the development of asthma and increased incidence in adults and children

In addition to potentiating each other's effects with other analgesics, paracetamol may also

potentiate the anticoagulant effect of warfarin (the interaction is due to the fact that paracetamol reduces the synthesis of vitamin K-dependent clotting factors). [5] Concomitant use of paracetamol may adversely affect the efficacy of antihypertensive therapy (with ramipril or valsartan). [13]

A large body of data on pregnant women indicates that paracetamol does not cause birth defects or is not toxic to fetuses or newborns. [3] In general, it is a recommended drug for pregnant women and their offspring. [12] In contrast, there is growing evidence of an association between paracetamol use during pregnancy and in newborns and an increased incidence of asthma, impaired mental and physical development and attention deficit hyperactivity disorder (ADHD), lung damage, bronchospasm, early closure of the ductus arteriosus, and preeclampsia. [11, 12] Cases of transplacental transfer of paracetamol after maternal overdose have also been described, but it is believed to be relatively safe in therapeutic doses. [4] Paracetamol is secreted into the milk of breastfeeding women in amounts that are not clinically significant. [3]

MATERIALS AND METHOD

Patient information was collected from hospital records available in the clinical toxicology department. In addition, we conducted a literature review on paracetamol treatment, its toxicity, side effects and pharmacokinetics using PubMed.

CASE REPORT

The patient, aged 16 years and 9 months, was brought from a hospital in Kraśnik and admitted to the Clinical Toxicology and Cardiology Department in Lublin due to paracetamol poisoning and suspected intoxication with a psychoactive substance. The patient's history showed that he had taken a total of 20 paracetamol 500mg (10g) tablets in short intervals of 2 h for abdominal pain. After several hours, nausea, profuse vomiting, and increased abdominal pain appeared. An initial dose of ACC (9.3g iv) was administered in Kraśnik hospital. Laboratory tests showed features of liver damage (ALT 383 U/l, AST 323 U/l, bilirubin 1.26 mg/dl, INR 1.25). At the time of admission to the local ward, the patient was conscious with logical verbal communication, cardiovascular and respiratory function, denied suicidal thoughts and intentional drug abuse. Laboratory tests showed acetaminophen about 18 hours after intoxication- 41.27 μg/ml, no psychoactive substances. A full dose of ACC was administered on the first day of treatment, and then, due to rapidly increasing parameters of liver damage, ACC infusion was continued at a maintenance dose and Legalon was

administered intravenously. The patient was consulted psychologically and psychiatrically with no indications for psychiatric hospitalization, and a follow-up at the Mental Health Clinic was recommended. On day 3 of hospitalization, due to rapidly increasing features of liver damage (INR 2.78, AST 6273 U/l, ALT 8854 U/l, bilirubin 3.83 mg/dl), the patient was consulted with the Gastroenterology Department of the Children's Health Center in Warsaw. In the following days, the aforementioned department was also consulted. Intensive treatment was maintained, which resulted in a downward trend in liver damage parameters (on the day of discharge ALT 318 U/l, AST 35 U/l, INR 1.15, bilirubin 1.21 mg/d, GGTP 140 U/l). The patient was discharged from the Ward in good general condition, without complaints.

DISCUSSION

Paracetamol is the most widely used over-the-counter analgesic drug in the world. [14] It is the only over-the-counter (OTC) drug reliably leading to death in overdose (NSAIDs are not). [12] In the late 1960s, it was realized that paracetamol poisoning could result in severe hepatotoxicity, liver failure, kidney failure and death. [14] According to recent information provided by the U.S. National Poison Data System (NPDS), paracetamol is one of the 25 drugs associated with the highest number of fatalities, either alone or in combination with other drugs. [6] An overdose of this drug can occur after a single ingestion of a large amount of paracetamol or a drug containing paracetamol, or after multiple ingestions of smaller amounts that eventually exceed the recommended total dose. [9] Many cases of paracetamol poisoning also result from the use of combination preparations with paracetamol, such as acetylsalicylic acid acetylsalicylic acid, codeine, oxycodone, propoxyphene, caffeine, dextromethorphan, antihistamines and expectorants. [6] Paracetamol is the pharmaceutical most commonly taken for intentional self-injury by adults and adolescents in Australia, the UK and other developed countries. [15] Poisoning most often occurs as a result of deliberate overdose of oral preparations (suicide poisoning). [16]

Unintentional overdoses, which are common in adults and children, are primarily due to therapeutic misuse and excessive dosing over a period of time; usually more than 3 days. [8]

Our patient denied that the paracetamol poisoning was due to a suicide attempt. He maintained that he took the drug every 5 minutes because of abdominal pain and headache. Seeing no improvement, he took another pill, for a total of about 20 pills. So far, he had not abused any medications, and he related the abdominal pain and headaches to sitting in front

of a computer for too long and not eating. The patient claimed that he did not realize the consequences of taking so much paracetamol. He was consulted psychiatrically and twice psychologically. with no indications for psychiatric hospitalization, follow-up at the Mental Health Clinic was recommended.

The main critical organ in acute poisoning is the liver (damage and necrosis of hepatocytes). [16] Both long-term use and acute overdose can cause liver damage. [9] Paracetamol overdose leading to liver damage, may end in liver transplantation or death. [3] A single dose of more than 10 g or 150 mg/kg to 200 mg/kg of paracetamol carries a risk of liver damage, but smaller doses can also cause liver damage, especially in chronic alcohol abusers or those suffering from anorexia. [14]

Paracetamol-induced hepatotoxicity is the leading cause of acute liver failure (ALF) in many high-income countries, including North America and the United Kingdom, and is reported in the United States as the leading reason for emergency liver transplants. [7, 10, 14] During the progression of ALF, the appearance of hepatic encephalopathy (HE) is indicative of deteriorating liver function. [8] In fatal cases in which paracetamol caused fulminant hepatic failure, the most common causes of death are cerebral edema or sepsis, in the early phase, and multiple organ failure in the later phase. [6] According to the American Association for the Study of Liver Diseases, the incidence of APAP-related liver toxicity has increased significantly in recent decades. [8] Acetaminophen toxicity occurs up to 8 hours after ingestion and is due to oxidation by CYP2E1 to N-acetyl p-benzoquinone (NAPQI), which is hepatotoxic and nephrotoxic. [7, 17] Ingestion of toxic amounts of acetaminophen overloads normal glucuronide and sulfate metabolic pathways. Increased glucuronides rapidly deplete any available glutathione, causing unbound NAPQI to bind to hepatocytes and cause cell necrosis.[7] Under certain conditions, APAP hepatotoxicity can occur even at therapeutic doses. There are a number of well-documented risk factors that lower the dose threshold for APAP toxicity. These include chronic alcohol consumption, concurrent use of other drugs that induce cytochrome P450 (CYP 450) enzyme activity, and malnutrition, which reduces the liver's stores of protective thiols. [8] Cases of liver failure have been reported in patients in glutathione-deficient states, especially in patients who are severely malnourished, suffer from anorexia, have a low body mass index (BMI) and regularly drink alcohol, or have sepsis. [3]

Paracetamol overdose also causes renal toxicity. [12]

Acetaminophen toxicity is characterized by four stages, determined in time after ingestion, which are placed in the table number 4 (Tab. 4.). [2, 7, 16, 18]

Table number 4 (Tab. 4.) Stages of paracetamol poisoning.

STAGES OF PARACETAMOL POISONING		
	TIME SINCE INGESTION OF PARACETAMOL	SYMPTOMS
STAGE 1	first 24 h	Most patients are asymptomatic. Nausea and vomiting may occur, less often abdominal pain, increased sweating, pallor and weakness, malaise. It is extremely rare for severe symptoms (coma, severe lactic acidosis) to occur as early as day 1 of poisoning - such a clinical course is characteristic of cases of massive drug overdose (75-100 g). At this stage, laboratory tests are usually normal. Liver necrosis begins to develop after this and can progress to acute liver failure.
STAGE 2	after 24 h to 72 h	Initially, the signs and symptoms of stage I subside and patients appear to improve clinically, while liver aminotransferases

		(AST, ALT) increase. As stage II progresses, patients develop pain and tenderness in the right upper quadrant of the abdomen and jaundice. Symptoms are accompanied by an increase in aminotransferases (ALT, AST), INR, bilirubin levels, hypoglycemia, metabolic acidosis, oliguria (rare), and renal dysfunction may occur.
STAGE 3	after 72 to 96 h	During this stage, signs and symptoms become more pronounced. Systemic symptoms, including malaise, nausea and vomiting, return and may be accompanied by central nervous system involvement, such as confusion, lethargy and possible coma. There is a peak increase in transaminases and INR, fulminant hepatic failure, hepatic encephalopathy, and hepatorenal syndrome. An increase in creatinine is usually observed between the 2nd and 5th day of

		poisoning.
STAGE 4	4 days to 2 weeks after ingestion (recovery phase) (death or organ regeneration)	Stage IV represents a period of resolution of liver damage. Liver regeneration/transplantation or death of the patient may occur. Death due to fulminant liver failure generally occurs between the 3rd and 5th day of poisoning. Other patients experience normalization of laboratory parameters and organ regeneration within 7-14 days.

Mortality from paracetamol overdose increases two days after ingestion, peaks on the fourth day, and then gradually decreases and mortality from severe liver failure is less than 5% with supportive care. Metabolic acidosis is the most important single indicator of likely mortality and the need for transplantation. [6, 18] Prompt recognition of acetaminophen toxicity is essential to reduce morbidity and mortality. [7]

Our patient took 10 g of paracetamol in quick succession. After a few hours, he developed nausea, profuse vomiting and increased abdominal pain. Features of liver damage (ALT 383 U/l, AST 323 U/l, bilirubin 1.26 mg/dl, INR 1.25) were already observed on the first day after taking acetaminophen. On admission of the patient to the Department of Toxicology and Cardiology in Lublin, the patient was conscious with logical verbal communication, cardiovascular and respiratory capacity, denied suicidal thoughts and intentional abuse of the drug. Body temperature was: 36.7 ℃, blood pressure: 129/80, heart rate: 77, weight : 75 kg, saturation: 99, number of breaths per minute: 12. The patient was tested for the presence of other psychoactive substances-cocaine, amphetamine, 6-monoacetylmorphine, cathinones, Mephedrone, EDDP-acid, methaqualone, MDPV, MDP, methamphetamine, opiates,

cannabinoids, ecstasy-in the urine, and they were not found in the patient's body. In laboratory tests, acetaminophen was 41.27 μg/ml about 18 hours after poisoning. According to Rumack and Matthew's nomogram, the patient had a high risk of liver damage already estimated at the time of admission.

On the 2nd day after paracetamol intoxication, the patient's well-being began to improve, he did not report pain, and on physical examination there was mild right lower abdominal pain. However, liver damage parameters began to increase. INR 1.86, AST: 516 U/l, ALT: 696 U/l, bilirubin: 3.08 mg/dl. On the 3rd day of hospitalization, due to rapidly increasing features of liver damage (INR 2.78, AST 6273 U/l, ALT 8854 U/l, bilirubin 3.83 mg/dl) and increasing right subcostal pain, the patient was consulted to the Gastroenterology Department of the Children's Health Center in Warsaw.

Treatment of paracetamol poisoning depends on the dose taken and the time at which the patient took paracetamol, as well as the patient's clinical condition. [14] Indications for hospitalization are placed in table number 5 (Tab. 5.). [2, 16].

Table number 5 (Tab. 5.) Indications for hospitalization in paracetamol poisoning.

INDICATIONS FOR HOSPITALIZATION IN PARACETAMOL POISONING
● taking a dose of >75 mg/kg in less than 1 h or impossible to determine (e.g., an unconscious patient) ● overdose of the drug for suicidal purposes (regardless of the declared dose) ● the occurrence of clinical signs indicating a toxic effect of the drug during its use ● patients who may have been forced to ingest the drug (regardless of the declared dose) ● Children < 6 years of age should be treated in a hospital setting if the single dose of paracetamol is unknown or is > 200 mg/kg. ● Children > 6 years and adults should be referred to hospital treatment if they have ingested paracetamol in a single dose of > 7.5 g and/or > 150 mg/kg, and when the amount ingested is unknown or difficult/impossible to determine. ● In case of acetaminophen poisoning in repeated supratherapeutic doses (RSI - Repeated Supratherapeutic Ingestion), the following are eligible for hospital treatment:

- children < 6 years of age if they have ingested:
  - > 200 mg/kg of paracetamol in one day.
  - > 150 mg/kg/day for the past 48 h.
  - > 100 mg/kg/day for the last 72 h or longer.
- Patients > 6 years of age if ingested:
  - With weight > 50 kg: > 4 g/day.
  - With weight < 50 kg: > 75 mg/kg/day.

Gastric lavage can be recommended to the patient within 1h after poisoning, and administration of activated charcoal p.o. (50 g in adults or 1 g/kg body weight) within 1-2 h after poisoning. [2, 16] Serum paracetamol concentrations should be determined 4 - 8 h after poisoning, and the result should be interpreted using a nomogram (e.g. Rumack and Matthew). [2] The Rumack-Matthew nomogram summarizes the relationship between the plasma concentration of acetaminophen (in micrograms/ mL or micromoles/L), the time since ingestion of the drug, and the risk of hepatotoxicity. It should only be used after a single acute ingestion of paracetamol. [7] If 8 - 24 h have elapsed since ingestion of the drug, a specific antidote should be started as soon as possible and serum paracetamol concentrations should be determined. Once the result is obtained, a decision should be made to continue or terminate the specific treatment. On the other hand, if > 24 h has elapsed since taking the drug, the administration of an antidote should be started as soon as possible. When biochemical tests performed on admission show no elevated values of AspAT, ALT, INR, specific treatment can be terminated.[2]

The specific antidote for paracetamol poisoning is N-acetylcysteine (NAC, ACC), which is almost 100% effective in preventing liver damage if given within eight hours of paracetamol ingestion. [18] It is a precursor in GSH synthesis, so its administration acts partly by restoring the intracellular GSH pool and partly by neutralizing residual NAPQI that is still present in the liver. [8] It can be administered orally or intravenously, but the intravenous route is preferred because of its shorter treatment time. [16] Indications for specific treatment with N-acetylcysteine are listed in table number 6 (Tab. 6.). [2]

Table number 6 (Tab. 6.) Indications for specific treatment with n-acetylcysteine.

INDICATIONS FOR SPECIFIC TREATMENT WITH N-ACETYLCYSTEINE	
If a single dose of the drug is taken	Have taken > 7.5 g or > 150 mg/kg of paracetamol.
	The poisoning was intentional and the dose taken cannot be reliably determined.
	Toxic serum levels of paracetamol were found within 4 - 24 h after poisoning.
	More than 24 h had passed since taking the xenobiotic and elevated transaminase values were found.
If multiple supratherapeutic doses are taken (RSI - Repeated Supratherapeutic Ingestion)	All patients with elevated transaminase activity.

All patients who have plasma paracetamol levels plotted at or above the curve drawn between 100 μg/ml at 4 hours after ingestion and 15 μg/ml at 15 hours should be given N-acetylcysteine. If there is doubt about the time of ingestion, N-acetylcysteine should be given immediately. [18] Treatment protocols for paracetamol poisoning vary around the world. [14] Table number 7 (Tab. 7.) shows the NAC administration regimens most commonly used in Poland. [2, 16]

Table number 7 (Tab. 7.) Treatment protocol with N-acetylcysteine.

PROTOCOL FOR INTRAVENOUS TREATMENT WITH N-ACETYLCYSTEINE (MODIFIED PRESCOTT PROTOCOL)	PROTOCOL FOR ORAL TREATMENT WITH N-ACETYLCYSTEINE
● The first dose of 150 mg/kg body weight (max 16.5 g) is administered after dissolving in 5% glucose or 0.9% NaCl within 15 - 60 min. In adult patients, the minimum volume of 5% glucose should be 200 - 500 ml, (unless there are contraindications, 500 ml is recommended), in children < 20 kg the volume is 3 ml/kg body weight, in children > 20 kg 100 ml. ● The next dose - 50 mg/kg body weight(max. 5.5 g) in 500 ml of 5% glucose or 0.9% NaCl - is given immediately after the first one in a continuous infusion lasting 4 h. ● The third dose - 100 mg/kg body weight (max. 11 g) in 1000 ml of 5% glucose or 0.9% NaCl - is given within 16 h immediately after the second. ● The second and third doses of N-acetylcysteine can be administered both by infusion pumps and by drip infusion. ● For a pregnant woman, calculate the NAC dose according to the current	● The first dose is 140 mg/kg body weight. Thereafter, 17 doses of the drug at 70 mg/kg body weight are given every 4 h. ● The total duration of treatment is 72 h. To facilitate the absorption of the drug, the antidote can be diluted in beverages. ● The total dose of N-acetylcysteine is 1330 mg/kg body weight.

body weight. ● The total dose of N-acetylcysteine is 300 mg/kg body weight	

The most common reactions after intravenous administration of acetylcysteine are nausea, vomiting and cutaneous systemic hypersensitivity reactions,and after oral administration are rash, nausea, vomiting, abdominal pain, stomatitis, fever, rhinitis, lethargy, petit mal, chest tightness and bronchoconstriction. Useful antiemetic drugs are 5-HT3 receptor antagonists, such as ondansetron, which can be administered to relieve nausea and vomiting. [7, 14]
After NAC i.v. administration, monitoring of laboratory parameters (INR, creatinine, blood gas, aminotransferases, electrolytes, lactate) is necessary. A chart for monitoring NAC therapy is included in table number 8 (Tab. 8.). [16]

Table number 8 (Tab. 8.) Monitoring NAC therapy.

MONITORING NAC THERAPY
● ALT <2 × upper limit of the standard or INR <1.3 → no need to continue NAC infusion ● ALT ≥2 × upper limit of the standard or doubling from baseline, or INR <1.3 → further treatment with NAC at a dose of 100 mg/kg body weight is necessary; after 8-16 h of NAC administration, recheck the above parameters. ● NAC therapy was started only due to features of liver damage → continue until INR ≤1.3 normalizes or decreases <3.0 in 2 consecutive determinations. ● High ALT activity with normal INR is not an indication for continuation of NAC therapy. Failure to normalize INR despite NAC therapy is a poor prognostic factor (risk of liver failure).

In 2011, a WHO panel reviewed the evidence, concluding that acetylcysteine and methionine

have the same efficacy and safety as an antidote for paracetamol poisoning. It is cheaper therefore has found widespread use in low- and middle-income countries such as Sri Lanka. [14]

In massive paracetamol overdose (serum concentrations >800 μg/ml) accompanied by coma and metabolic acidosis, urgent hemodialysis should be considered, with at least a 2-fold increase in the dose of NAC. [16]
In some cases, treatment involves liver transplantation. The King's College criteria for deciding on liver transplantation are listed in table number 9 (Tab. 9.). [2]

Table number 9 (Tab. 9.) King's College Criteria.

KING'S COLLEGE CRITERIA
Serum lactate level > 3.5 mg/dL (0.39 mmol/L) after attempting 4 h to compensate for water-electrolyte disturbances; OR pH < 7.30 or serum lactate level > 3.0 mg/dL (0.33 mmol/L) after attempting 12 h of equilibration of water-electrolyte disturbances; OR INR > 6.5 [PT (prothrombin time) > 100 sec], serum creatinine level > 3.4 mg/dl (300 mmol/l) and grade 3 or 4 hepatic encephalopathy.

Due to the fact that the patient had already taken 10 g of paracetamol in the hospital in Krasnik, an initial dose of ACC was administered (9.3 g iv). According to Rumack and Matthew's nomogram, the patient had a high risk of liver damage already estimated at the time of admission. After the patient was admitted to the Department of Toxicology and Cardiology in Lublin, the patient received a full dose of ACC on the first day of treatment, and then, due to rapidly increasing parameters of liver damage, the ACC infusion was continued at a maintenance dose and Legalon was administered intravenously. An easily digestible diet with fat restriction (hepatic) was implemented.
On day 3 of hospitalization, due to rapidly increasing features of liver damage (INR 2.78,

AST 6273 U/l, ALT 8854 U/l, bilirubin 3.83 mg/dl), the patient was consulted with the Gastroenterology Department of the Children's Health Center in Warsaw. In the following days, the aforementioned department was also consulted. The prescribed intensive treatment was maintained (continuation of ACC infusion and 10 mg Vit.K), thanks to which a decreasing trend in liver damage parameters was achieved (on the day of discharge ALT 318 U/l, AST 35 U/l, INR 1.15, bilirubin 1.21 mg/dl, GGTP 140 U/l). In the absence of improvement after the applied treatment, the patient would be qualified for liver transplantation. The patient was discharged from the Department in good general condition, without complaints.

Many experts believe that paracetamol would not be allowed on the market today. [12] Because paracetamol is readily available in over-the-counter products, unintentional overdoses occur because most consumers do not have the knowledge or do not take the trouble to read which preparations contain APAP, or they may not be informed or understand the concept of the maximum recommended daily dose, or are unaware of the potential for hepatotoxicity with excessive dosing, despite warnings and dosage recommendations on the label or in the package insert. [8] Due to the increasing number of paracetamol overdoses, the U.S. Food and Drug Administration (FDA) in 2009 asked for the elimination of drugs containing paracetamol-related products, and in 2011 determined that all drugs containing paracetamol in combination should not exceed 325 mg of paracetamol per tablet making the total daily dose of paracetamol 2600 mg if eight tablets are taken daily. In addition, the FDA has stated that it is crucial that packaging be labeled with information about the risk of liver damage caused by excessive use of the drug, that the international name be used, and that all preparations containing paracetamol, that they carry an alcohol warning. Unfortunately, this labeling is not required in other countries. The FDA has suggested the need to withdraw from the market all combination drugs, both over-the-counter (OTC) and prescription, because they are largely responsible for acute paracetamol poisoning, according to various studies. [5, 6] Given the impulsive nature of many paracetamol overdoses, preventive measures that limit the size of paracetamol packages and reduce the risk of ingesting larger, toxic amounts, are of great interest. [15] Patient education, promoting awareness, encouraging label reading (including OTC products) are very important elements of strategies to spread awareness of possible paracetamol overdose. [6, 7] Most likely, if our patient had read the leaflet, someone would have informed him earlier about the harmful effects of taking too much paracetamol, or if there were fewer pills in the package an overdose would have been avoided.

CONCLUSION

Due to the increasing number of paracetamol overdoses (intentional or accidental), awareness and prevention strategies should be implemented. Patient education, encouraging label/leaflet reading, reducing the amount of paracetamol in packages, and more visible warnings on packages seem to be good ideas. It will take time for most countries to implement such solutions.

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