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Modification of antidote therapy for poisoning due to massive admission of paracetamol

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Abstract

Background. *Paracetamol poisoning is common all over the world, including in Russia. In 20–25% of cases, a massive dose of the drug is observed: more than 30–40 g of paracetamol at a time.*

The aim *of the study was to demonstrate the efficacy of using an increased doses of acetylcysteine in the treatment of a massive paracetamol admission.*

Results. *Patient G., 22 years old, took 70 tablets (35 g) of paracetamol for suicide 3 hours before admission to the hospital. The blood level of paracetamol 4 hours after taking it was 694.94 μg/mL. Upon admission*

to the hospital, acetylcysteine administering was started according to a 12-hour scheme. Subsequently, the administration of acetylcysteine was continued according to a 20-hour regimen with an increased dosage at the 2nd stage. Laboratory parameters, including aspartate aminotransferase and alanine aminotransferase, remained within the reference values during hospital stay.

Conclusion. *The case report we have presented shows the efficacy and expediency of using an increased doses of acetylcysteine in case of massive admission of paracetamol, which contributes to the prevention of the development of severe complications and a favorable course and outcome of the disease.*

Keywords: paracetamol poisoning, treatment, acetylcysteine, antidote therapy

Conflict of interests Authors declare no conflict of interest

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ACC, acetylcysteine
ALT, alanine aminotransferase
AST, aspartate aminotransferase
CTI, chemical-toxicological investigation
FLF, fulminant liver failure
i.v., intravenously

Introduction

Paracetamol (acetaminophen) is the most commonly used drug in the world. It is an over-the-counter, affordable drug that has analgesic and

antipyretic effects. The wide availability of the drug is due to its relative safety when taking therapeutic doses, however, in various countries, paracetamol overdose is the most common cause of liver damage, requiring transplantation in some cases [1]. According to the literature, in the UK, paracetamol ranks 3rd in the structure of acute poisoning as its cause, 50,000 cases of paracetamol poisoning occur annually; in the United States, 80,000 calls for paracetamol poisoning are recorded every year, of which 30,000 cases require hospital admission [2]. Australia is facing a 44.3% increase in annual hospital admissions for acute paracetamol poisoning from 8,147 cases in 2007-2008 up to 11,754 cases in 2016–2017 [3]. An overdose of paracetamol was the cause of the development of acute liver failure in 50% of cases, registered over the past 40 years in the United States and Europe [4].

Hepatotoxic effect in cases of a paracetamol overdose is the result of the accumulation of N-acetyl-para-benzoquinone imine, which lacks time to be neutralized by the liver glutathione as a result of the depletion of its reserves. A toxic metabolite begins to bind covalently to hepatocyte proteins, causing their arylation and then death [5]. The outcome may be the development of fulminant liver failure (FLF). Liver transplantation is the only effective treatment for the development of FLF. To date, in order to determine the indications for liver transplantation in case of paracetamol poisoning, the criteria developed at the Royal College Hospital (UK) are used, namely: blood pH lower than 7.3, prothrombin time more than 100 s, serum creatinine level more than 300 μmol/L and stage III-IV liver encephalopathy [6, 7].

To assess the risk of liver damage, the Rumack-Matthew 100/150/200 nomogram is used, when the indicators such as the serum concentration of paracetamol and the time from the moment of taking the drug are known. A nomogram is a graphical representation of the toxic

concentrations of paracetamol in the blood from 4 to 24 hours after taking it. The risk of hepatotoxicity is assessed along three “treatment” lines: the 1st line from 150 μg/mL after 4 hours (hepatotoxicity line for healthy people with a bias for an error in anamnestic and laboratory data), the 2nd one from 100 μg/mL after 4 hours (hepatotoxicity line for patients with a high risk of developing liver damage, suffering from liver diseases, chronic alcohol intoxication, anorexia, etc.), the 3rd line from 200 μg/mL after 4 hours (probable hepatotoxicity line for healthy people) [5, 8]. If the "treatment line" according to the Rumack-Matthew nomogram is exceeded, there is a high risk of hepatotoxicity, which is an indication for antidote therapy. If there is no data on the time of taking the drug or it is not possible to determine its blood serum concentration, then it is necessary to focus on the dose of the drug taken and the laboratory indicators of liver damage. In case of taking a toxic dose of paracetamol, it is necessary to immediately begin administering an antidote until chemical-toxicological confirmation has been obtained [9]. It is known that the time interval from taking the drug to the start of the antidote administration exceeding 8 hours is one of the main factors of a high risk for developing liver damage [9].

The complex of treatment for acute paracetamol poisoning includes infusion therapy, enterosorption in the first 4 hours after taking the drug, antidote and symptomatic therapy [8]. Acetylcysteine (ACC) is an effective antidote for paracetamol poisoning. It prevents the development of hepatotoxicity mainly due to the replenishment of glutathione, which in turn converts N -acetyl-p-benzoquinone imine into non-toxic paracetamol conjugates. At later stages, ACC changes the course of the inflammatory response that develops when a toxic metabolite binds to the structural proteins of the liver. ACC has an antioxidant effect, is a source of sulfhydryl groups, increases the activity of nitric oxide synthase,

combines with nitric oxide to form a potent vasodilator, and promotes the formation of the most important endogenous antioxidants, including glutathione [10].

Currently, the efficacy and safety of a number of schemes for the ACC administration in paracetamol poisoning have been proven. The classic options are: a 21-hour intravenous (i.v.) protocol in three stages (total dose 300 mg/kg), a 20-hour i.v. protocol in two stages (total dose 300 mg/kg), and a 72-hour peroral protocol (1330 mg/kg) [8, 9]. In a number of countries, a 12-hour intravenous protocol is used in two stages (total dose of 300 mg/kg) [11, 12].

There are a number of difficult situations with paracetamol poisoning, leading to a change in the standard treatment regimen [1]. One such case is a massive overdose of paracetamol, occurring in 20–25% of cases [1]. We should note that there is no established definition of a massive overdose. According to a number of authors, a massive intake is more than 30–40 g of paracetamol, while its blood level is more than 2 times higher than the “treatment” line according to the Rumack-Matthew 150 nomogram [5, 13, 14]. A.L. Chiew et al. found that in 14% of cases of massive paracetamol poisoning, liver damage developed despite the ACC administration according to the standard protocol in the first 8 hours from the moment of intake [13]. A number of authors suggest an increase in the ACC dose in this situation; there have also been described cases of using hemodialysis [5, 15]. However, researchers have no univocal opinion.

Below we represent our own clinical case report of the treatment for paracetamol poisoning with massive doses.

The aim was to demonstrate the efficacy of using an increased acetylcysteine doses with massive intake of paracetamol.

Clinical Case Report

Patient G., 22 years old, was delivered to the Toxicology Department of the N.V. Sklifosovsky Research Institute for Emergency Medicine with the diagnosis of "Poisoning with paracetamol". From the medical history, it became known that 3 hours before the admission to the hospital, she simultaneously took 70 tablets of paracetamol 500 mg (35 g) with the aim of suicide. At the prehospital stage, gastric tube lavage and infusion therapy were performed. On admission, the patient was in a clear mind (scored 15 by Glasgow Coma Scale); no hemodynamic or respiratory disorders were observed. The patient complained of weakness. The patient was hospitalized to the Toxicological Intensive Care Unit for performing an intestinal lavage, infusion detoxification, antidote and symptomatic therapy. The decision was made to immediately start a 12-hour protocol of intravenous ACC administration according to the following scheme: 100 mg/kg in 200 ml of 5% glucose for 2 hours at the 1st stage; 200 mg/kg in 1000 ml of 5 % glucose for 10 hours (total dose 300 mg/kg) at the 2nd stage. Antidote therapy was started before the results of a chemical-toxicological investigation (CTI) were obtained, since it was known that the patient had taken a toxic dose (more than 7.5 g for adults) of 35 g. The treatment complex also included an intestinal lavage in a volume of 4.5 liters. Saline enteral solution of the temperature 18-22^{o}C, was administered per os every 5 minutes, 200 ml each.

Four hours after taking paracetamol, a quantitative determination of the drug in blood was performed by chromatography-mass spectrometry on an Agilent 7890 B device with a 5977B mass selective detector after extraction from blood. It is known that the serum concentration of paracetamol should be determined no earlier than 4 hours after taking the drug [10]. The blood level of paracetamol was

694.94 μg/mL. After determining the paracetamol concentration in blood, the Rumack-Matthew 150 nomogram was used to assess the risk of liver damage: a straight line ("treatment" line) starts at 150 μg/mL (4 hours after intake), passes through 37.5 μg/mL (after 12 hours) and ends at the point of 4.7 μg/mL (after 24 hours) [10]. The "treatment" line corresponds to the critical values of the paracetamol concentration in blood, at which the risk of liver damage is high and the use of antidote therapy is necessary. In the patient, the blood level of paracetamol exceeded the "treatment" line by 4.6 times, which indicated a very high risk of liver damage. The following laboratory parameters were assessed: blood levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), international normalized ratio, and the parameters of the blood acid-base state throughout the entire in-hospital period.

Upon completion of the intravenous ACC administration according to a 12-hour protocol, the serum level of paracetamol and the concentrations of ALT and AST in blood were re-quantified. According to the literature, indications for continuing the antidote therapy are the data indicating liver damage (ALT and AST activities of more than twice higher than the reference values) or an incomplete elimination of paracetamol (serum concentration of more than 20 μg/mL). At repeated CTI, the concentration of paracetamol (acetaminophen) in blood was found to be 390 μg/mL, ALT 48.11 U/L, AST 47.57 U/L, other blood markers of liver damage were within the reference values. The decision was made to use a 20-hour 2-stage intravenous administration of ACC with an increased dose at the 2nd stage: 200 mg/kg for 4 hours at the 1st stage, 200 mg/kg for 16 hours (total dose of 400 mg/kg) at the 2nd stage. At the end of the 20-hour protocol for the ACC administration, no paracetamol was detected in blood, laboratory parameters were within

the reference values. Intravenous administration of ACC was discontinued. The patient was transferred to the Department of Acute Poisoning for further observation and subsequently discharged in a satisfactory condition. The hospital length of stay was 3 days.

Figure 1 shows the changes of ALT and AST concentrations in the patient's blood throughout the entire observation period.

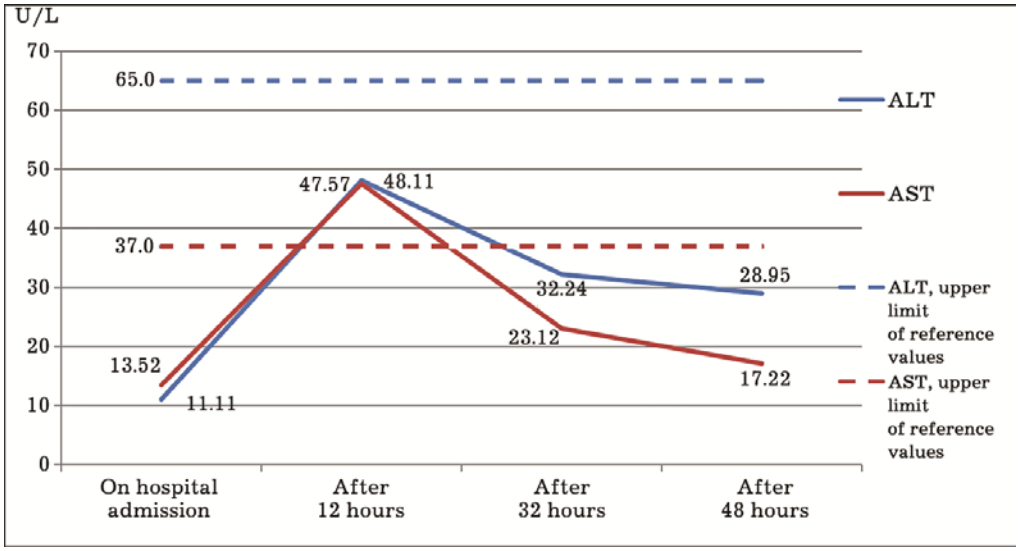

Fig. 1. Dynamics of alanine aminotransferase and aspartate aminotransferase levels in blood. The study was performed on Sapphire 400 analyzer.

Discussion

According to the literature, a massive paracetamol overdose after taking leads to prolonged absorption of the drug, setting its consistently high concentrations in blood with its repeated "peaks" [13, 16].

The use of the standard scheme of early intravenous administration of the ACC antidote (total 300 mg/kg) in some cases showed insufficient efficacy in such case [1, 13, 17]. In order to solve this problem, a number of studies were conducted that brought about the proposed new schemes for the use of ACC, with a change in the dose and duration of the antidote

administration. Thus, a study conducted in patients who had taken a high dose of paracetamol (30 g or more), and having its concentration twice exceeding the “treatment line” of the nomogram showed that the standard scheme modification for the ACC administration, in which the total dose of ACC is 400–500 mg/kg, may reduce the risk of hepatotoxicity within 21-22 hours. However, the impact of this approach on the development of liver failure, the need for liver transplantation, and mortality is currently unknown [10]. A.L. Chiew et al. proved that in patients with a massive paracetamol overdose who were administered an increased dose of ACC (twice increased up to 200 mg/kg for 16 hours during the third stage of the 21-hour protocol, a total of 400 mg/kg), the risk of hepatotoxicity was significantly lower (odds ratio [OR]: 0.27; 95% confidence interval [CI] 0.08–0.94) [13]. The guidelines in a number of countries prescribe an increase by 2 times in the antidote dose in case of massive poisoning, and performing hemodialysis, if necessary. The literature reports clinical cases showing the efficacy of hemodialysis in case of poisoning associated with massive intake of paracetamol [18, 19].

In our case, the patient took 70 tablets of paracetamol (35 g), the blood level of the drug was initially 694.94 μg/mL at 4 hours after the intake. No activated charcoal was used at the prehospital stage. Meanwhile, the study by A.L. Chiew demonstrated that taking activated charcoal within 4 hours from the moment of the drug intake contributed to a significant decrease in the initial paracetamol concentration in blood and influenced its subsequent absorption [13]. Upon the patient admission to hospital, the antidote administration according to a 12-hour scheme was started without waiting for CTI results, considering the taken drug dose of 35 g. This choice was made due to the fact that an early ACC administration (in the first 8 hours), as a rule, leads to a complete recovery [10]. According to the SNAP study, the 12-hour protocol,

despite a similar total dose of ACC (300 mg/kg), has a number of advantages: fewer allergic reactions during its implementation, the chance to start quickly (after 12 hours) the next dose of the antidote, if indicated [12]. Due to the fact, after the 12-hour protocol completion, the patient still had the indications for further ACC administration (the blood paracetamol concentration of 390 μg/mL), a 20-hour standard protocol was applied with an increase in the dose at the second stage (total dose of 400 mg/kg).

Thus, the consecutive administration of ACC according to the 12- and 20-hour protocols we used with an increase in the dose at the second stage in the case of poisoning with a massive paracetamol dose had a favorable effect on the disease course and the outcome. Extracorporeal detoxification was not required.

Conclusion

The case report we have presented demonstrates the efficacy and expediency of using an increased dose of acetylcysteine in case of poisoning with massive doses of paracetamol, which contributes to the prevention of severe complications and a favorable course of the disease and the outcome.

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