**Research Article**

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# On the Treatment of Acute Poisoning With Paracetamol

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**BACKGROUND** Currently, despite the optimization of diagnostic methods in order to predict the development of liver damage, improvement of treatment protocols, paracetamol poisoning is a serious problem in medicine, being the most common cause of acute liver failure worldwide.

**AIM OF STUDY** To determine the indications for the use of acetylcysteine in paracetamol poisoning and evaluate the effectiveness of the 21-hour protocol for its administration.

**MATERIAL AND METHODS** We examined 20 patients with acute paracetamol poisoning (15 women and 5 men), the median age was 21.5 (19.8–32.3) years. ALT and AST were assessed during the entire period of stay in the hospital, the time period from the moment of taking paracetamol to hospitalization and the beginning of the administration of ACC, the concentration of paracetamol in the blood, and mortality. According to the level of ALT and AST in the blood, the patients were divided into 2 groups: Group I consisted of 14 patients, in whom the concentration of ALT and AST during the entire observation period did not exceed 50 U/L; in Group II (6 patients), an increase in the level of ALT and AST in the blood of more than 50 U/L was observed. To assess the risk of liver lesion, the Rumack-Matthew nomogram was used. To compare the concentrations of paracetamol in the blood of patients, the paracetamol index was used.

**RESULTS** It was found that in 10 patients with a high risk of liver damage, who were treated with a 21-hour regimen of ACC administration, no hepatotoxic effect was found. The use of ACC according to a 21-hour protocol in patients with initially elevated ALT and AST levels of more than 50 U/L (n = 4) (25%) led to a rapid positive dynamics of laboratory and clinical parameters. It was found that in 2 patients, despite the introduction of ACC, the development of liver damage was observed. At the same time, the level of paracetamol in their blood was 6.6 and 10.6 fold higher than the "therapeutic" line of the nomogram, and the time from the moment of taking the drug to the beginning of the administration of ACC was 8 and 20 hours. High risk factors for the development of hepatotoxic effect in case of paracetamol poisoning are the time range from the moment of taking the drug to the beginning of the administration of ACC and the value of the paracetamol index.

**CONCLUSION** Indications for the use of acetylcysteine in acute poisoning with paracetamol is a high risk of liver damage. Its criteria are high doses, increased concentrations of ALT and AST when patients are admitted to the hospital; if it is possible to determine the concentration of paracetamol in the blood, an increase in the value of the paracetamol index is more than 1. The use of a 21-hour protocol of intravenous administration of acetylcysteine is effective in case of paracetamol poisoning and its early use in the complex of treatment almost always prevents the development of acute liver failure.

**Keywords:** cerebrospinal fluid, phase-contrast MRI, cerebrospinal fluid dynamics

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ACC – acetylcysteine
ALT – alanine aminotransferase
AST – aspartate aminotransferase
ICU – intensive care unit
IL – intestinal lavage
INR – international normalized ratio
PI – paracetamol index

## BACKGROUND

Paracetamol (acetaminophen) is an over-the-counter analgesic and antipyretic drug widely used in all countries in the form of numerous dosage forms for monotherapy, as well as in combination with non-steroidal anti-inflammatory drugs, analgesics, antihistamines and other drugs [1].

Currently, paracetamol poisoning (ICD-10-T39.1) is an urgent problem of toxicology due to a significant increase in the number of cases worldwide [2]. In the UK, USA, Australia and several European countries, paracetamol poisoning is the most common cause of acute liver failure requiring liver transplantation [3]. In the Russian Federation, on the contrary, until recently, paracetamol poisonings accounted for a rather modest share in the overall structure of exotoxicoses. So, their share in 2008 was 0.67% among all poisonings and 18.4% in group T39 "Analgesic, antipyretic and antirheumatic drugs" [4]. However, the number of paracetamol poisonings has increased recently due to the appearance on the domestic pharmaceutical market of a large number of various dosage forms containing paracetamol, including long-acting ones, under different trade names [4, 5].

When intoxicated with paracetamol, under the action of microsomal liver enzymes, a toxic metabolite *N*-acetyl-*n*-benzoquinoneimine is formed. When taken in a therapeutic dose, it is completely inactivated by reduced glutathione with the formation of non-toxic metabolites. During intoxication, the accumulation of *N*-acetyl-*n*-benzoquinoneimine occurs faster than the reduction of glutathione, the metabolite begins to covalently bind to hepatocyte proteins, causing their arylation and, as a result, necrosis [6]. After ingestion of toxic doses of paracetamol, absorption occurs within 2 hours, the maximum serum concentration is reached within 4 hours. It has been established that the toxic dose of paracetamol is 7.5 g in adults and 150 mg/kg in children [6]. A number of authors indicate that a hepatotoxic effect is already possible when taking the drug at a dose of 4-5 g in adults or 125 mg / kg in children with concomitant liver diseases, constant use of drugs, especially those that are inducers of cytochrome *P* 450 (barbiturates, isoniazid, rifampicin, diphenin, etc.), dietary supplements, anorexia, etc. [6, 7].

Acetylcysteine (ACC) is known to be an effective antidote for paracetamol poisoning. It replenishes glutathione reserves and binds to a toxic metabolite with its subsequent transformation into non-toxic compounds with cysteine and mercaptopurine acid [6]. In recent years, the use of various schemes for the introduction of ACC has been of great interest [7–10]. Modern approaches to solving this problem are related to issues related to the route and duration of ACC administration, its safety, and effectiveness. Contradictory data are also found in the literature regarding the use of activated carbon [11, 12]. Different countries use different protocols for the treatment of paracetamol poisoning. The lack of convincing data on the optimal complex for the treatment of acute paracetamol poisoning prompted us to conduct this study.

**Aim of study:** to determine the indications for the use of ACC in paracetamol poisoning and to evaluate the effectiveness of the 21-hour protocol for its administration.

## MATERIAL AND METHODS

A retrospective observational study was carried out on the basis of the Department of Acute Poisoning and Somatopsychiatric Disorders of the N.V. Sklifosovsky Research Institute for Emergency Medicine for the period of April-September 2021. We examined 20 patients with acute paracetamol poisoning who were admitted to the hospital after a single-stage intake of Paracetamol tablets or combined drugs containing the active substance paracetamol (Trigan D, Pentalgin, Citramon) at a dose of more than 7.5 g. (Table 1). The study included 15 women (75%) and 5 men (25%). The median age of patients was 21.5 (19.8–32.3) years, *min* — 16 years, *max* — 71 years.

Endpoints of the study: the level of alanine aminotransferase (ALT), aspartate aminotransferase (AST), international normalized ratio (INR) in the blood throughout the entire period of stay in the hospital, the time range between the moment of taking paracetamol and hospitalization with the initiation of ACC administration, the concentration of paracetamol in blood and mortality. According to the level of ALT and AST in the blood, the patients were divided into two groups: group I consisted of 14 patients in whom the concentration of ALT and AST during the entire observation period did not exceed 50 U/l; in patients of group II (6 patients), an increase in the level of ALT and AST in the blood by more than 50 U/l was noted.

The concentration of paracetamol in the blood of all patients was determined upon admission to the hospital by chromato-mass spectrometry by Agilent 7890 B device with a 5977B mass selective detector after extraction from the blood. Repeated paracetamol blood test was performed in patients who also had introduction of ACC in the complex of treatment (21 hours after the start of administration).

After determining the concentration of paracetamol in the blood to assess the risk of liver damage in our study, we used the Ramack–Mathew 150 nomogram (Fig. 1) [12]. It can be seen from the figure that the direct (“treatment”) line starts at 150 μg/ml (4 hours from the moment of administration), passes through 37.5 μg/ml (in 12 hours) and ends at the point 4.7 μg/ml (in 24 hours). The "treatment" line corresponds to the critical values of the concentration of paracetamol in the blood, at which the risk of liver damage is high and the use of antidote therapy is necessary [13]. The nomogram was used in patients who had paracetamol levels in their blood between 4 and 24 hours after taking it. When constructing the nomogram, the half-life of paracetamol was assumed by the authors to be 4 hours [6, 14, 15].

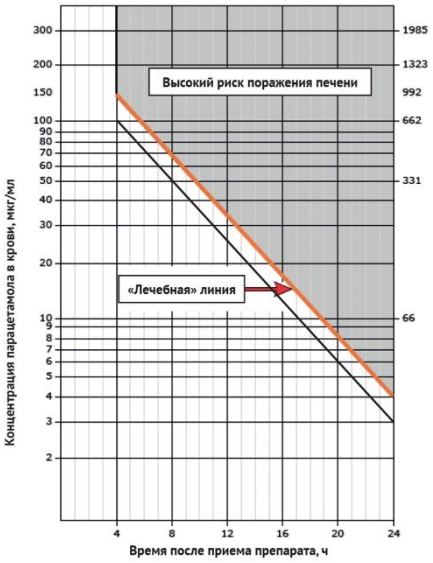


Fig. 1. Rumack-Matthew nomogram for determining the risk of liver damage in acute paracetamol poisoning

To compare the concentration of paracetamol in the blood of patients, the paracetamol index (PI) was calculated, due to the fact that the time range from the moment of taking the drug to the chemotoxicological study was different for each patient. PI for each patient was calculated as the ratio of the serum concentration of paracetamol to the level of paracetamol corresponding to the "treatment" line according to the Rumack-Matthew 150 nomogram at a given time.

$$\text{Paracetamol Index} = \frac{\text{Serum concentration of paracetamol}}{\text{Serum concentration of paracetamol, blood, corresponding to the "treatment" line of the Rumack-Matthew nomogram at this time}}$$

ACC was administered intravenously (i.v.) in the 21-hour regimen for patients in whom the concentration of paracetamol was higher than the "treatment" line according to the Rumack-Matthew nomogram 150 or PI more than 1. The introduction of ACC was carried out in three stages: 1 — saturating dose of ACC in the first 60 minutes (150 mg / kg), 2 — maintenance dose of 50 mg/kg for 4 hours, 3 — 100 mg/kg for 16 hours. The total dose of ACC was 300 mg/kg. If a paracetamol concentration in the blood of more than 10 μg/ml was detected again 21 hours after the initiation of ACC administration or an increase in the blood level of ALT and AST by more than 2-fold, the intravenous administration of ACC was continued according to a 21-hour protocol.

Statistical processing of the material was performed using the *IBM SPSS Statistics* 26.0 program. The normality of data distribution was assessed using the Shapiro–Wilk test ($n \leqslant 50$). With a normal distribution, the arithmetic mean (M) and standard deviation (SD) were determined. For non-parametric data, the median (Me), $25^{th}$ and $75^{th}$ percentiles were determined as Me ($Q_1$-$Q_3$). The categorical data were presented as n (%). The comparison of quantitative data between groups was performed using the Mann–Whitney test (cr. M–W) (independent groups). To assess the strength of relationships between various indicators, a correlation analysis was performed with the calculation of the Spearman correlation coefficient (rho). The significance level was taken at $p < 0.05$.

## RESULTS

The results obtained indicated that the median time from the moment of oral administration of paracetamol to hospitalization was 5 (2.88–12.5) hours (Table 1). The median of the paracetamol dose when taken per os was 15.5 (10.0–21.9) grams.

*Table 1*

**Characteristics of patients with acute paracetamol poisoning**

| Indicators | Values |
|---|---|
| Number of patients | twenty |
| Age, years, Me ($Q_1$–$Q_3$) | 21.5 (19.8-32.3) |
| Weight, kg M±SD | 59.3±10.9 |
| Taken dose of paracetamol, g Me ($Q_1$–$Q_3$) | 15.5 (10.0–21.9) |
| Taken dose of paracetamol, g/kg Me ($Q_1$–$Q_3$) | 0.29 (0.16–0.43) |
| Alcohol intoxicated patients, *n* (%) | 3 (15) |
| Patients with combined use of paracetamol and other drugs, *n* (%) | 6 (30) |
| Time between intake and hospitalization, hours Me ($Q_1$–$Q_3$) | 5 (2.88–12.5) |
| Paracetamol index, Me ($Q_1$–$Q_3$) (*n* =16) | 1.86 (0.93–3.6) |
| The level of ALT, AST upon admission to the hospital <50 U/l, *n* (%) | 16 (80) |

Notes: ALT — alanine aminotransferase; AST — aspartate aminotransferase

At the time of admission to the hospital, patients complained of nausea, vomiting in 80% of cases (*n* = 16), 17 patients (85%) complained of dizziness, in 25% of cases (*n* = 5) patients noted the presence of headache, in one patient icterus of the sclera was observed. In 2 cases, depression of consciousness to moderate coma (score 6-8) was revealed according to the Glasgow Coma Scale. They were diagnosed with combined poisoning with paracetamol and psychopharmacological drugs.

The median paracetamol index was 1.86 (0.93–3.6) (*n* =16). In 4 patients, this indicator was not calculated for the following reasons: in 2 patients, for technical reasons, the concentration in the blood of paracetamol could not be determined; in 2 patients, more than 24 hours passed from the moment of taking paracetamol to hospitalization, and therefore the Rumack-Matthew nomogram was not used. In 12 patients (60%), the paracetamol index was more than 1, thus, the initial concentration of paracetamol exceeded the "treatment" line according to the Rumack-Matthew 150 nomogram, while in 7 (35%) more than 2-fold (PI> 2). In 4 patients, the paracetamol index was less than 1 (0.64; 0.16; 0.3; 0.26), which indicated that the content of paracetamol in the blood was below the “treatment” line according to the Rumack–Matthew 150 nomogram and a low risk of liver injury.

In a chemical-toxicological study, in 6 cases (30%) psychopharmacological drugs (phenobarbital, chlorprothixene, finlepsin, etc.), salicylates were qualitatively detected in the blood. In 3 patients, ethanol was found in biological media (in g/l): 0.69 in urine and 1.32 in blood; 2.06 in urine and 3.2 in blood; 1.44 in urine and 2.17 in blood.

Information about the methods of treatment of patients with paracetamol poisoning is given in Table 2.

*Table 2*

**Methods of treatment of patients with paracetamol poisoning**

| Indicators | Values |
|---|---|
| Gastric lavage, *n* (%) | 13 (65) |
| The introduction of activated carbon, *n* (%) | 7 (35) |
| Intestinal lavage, *n* (%) | 20 (100) |
| Introduction of ACC according to the 21-hour protocol, *n* (%) | 16 (80) |
| 2-fold administration of ACC according to the 21-hour protocol (42 hours), *n* (%) | 6 (30) |
| 3-fold administration of ACC according to the 21-hour protocol (72 hours), *n* (%) | 1 (5) |
| Time before treatment with ACC, hours Me ($Q_1$–$Q_3$) | 11.0 (8.0–18.5) |

Note: ACC — acetylcysteine

As can be seen from Table 2, gastric lavage at the prehospital stage (3–9 hours after taking the drug) was performed in 13 patients (65%). It was found that they have a median paracetamol index of 2.55 lower than in those patients who did not use it (1.22 (0.61-2.58) versus 3.12 (2.16-3.6) ($p$ <0.05).The complex of treatment in 7 patients included the use of activated charcoal at the prehospital stage, while only in 3 cases it was administered in the first 4 hours. PI in these patients was 3.3, 6.6 and 1.86.

In 100% of cases, upon admission to the hospital, tubeless intestinal lavage (CL) was performed using an enteral solution [4]. The total volume of the solution ranged from 3 to 4.5 liters. The CL procedure lasted an average of 3 hours. Patients tolerated it satisfactorily, there were no reactions or complications.

The introduction of ACC was included in the complex therapy in 16 patients (80%). In 4 cases, due to the low content of paracetamol in the blood (below the "treatment" line), ACC was not used. Liver damage was not subsequently observed in these patients. The median time from the moment of taking paracetamol to the start of ACC administration was 11.0 (8.0–18.5) hours. In one case (5%), the administration of ACC was stopped in 1 hour due to the development of an allergic reaction in the form of a papular rash. An hour later, the introduction of ACC was resumed at a rate of 50 mg/kg, an allergic reaction was not observed again. In 6 cases (30%), intravenous infusion of ACC was continued after a 21-hour regimen (42 hours) due to an increase in ALT and AST content in the blood by more than 2-fold compared to the reference values or the detection of a serum paracetamol concentration of more than 10 μg/l after 21 hours after the start of the ACC. In one patient, a 21-hour regimen of ACC administration was performed 3 times due to a significant increase in the level of ALT, AST and a change in indicators indicating liver damage.

The results obtained showed that in 6 patients (30%) with paracetamol poisoning, the development of a hepatotoxic effect was observed. As can be seen from Table 3, there is a large range of the presented indicators, which makes it impossible to identify the leading criteria for the risk of liver damage in case of paracetamol poisoning.

The results of a comparative assessment of the factors influencing the development of the hepatotoxic effect and the duration of treatment between groups of patients whose ALT and AST levels were less than 50 U/l (group I) and more than 50 U/l (group II) during the observation period are presented in Table 4.

*Table 3*

**General characteristics of patients with the development of a hepatotoxic effect in paracetamol poisoning**

| Patient, age | Gender | Weight, kg | Time between intake and hospitalization, h | Taken dose of paracetamol, g | Paracetamol index | Intake of others toxicants | ALT level upon admission to the hospital, U/l | AST level upon admission to the hospital, U/l | Time before the start of ACC administration, h | Number of ACC protocols | Methods of artificial detoxification | Peak ALT, U/l | Peak AST, U/l | Peak INR |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| K., 18 years old | f | 50 | 10 | 18 | 1.22 | – | 56.44 | 86.9 | 11 | 2 | – | 826.16 | 584.76 | 1.77 |
| K., 23 years old | m | 67 | 3 | 20 | 6.6 | – | 10.61 | 15.91 | 8 | 2 | – | 898.59 | 599.67 | 1.53 |
| V., 34 years | f | 53 | 48 | 10 | – (paracetamol concentration at admission 7.71 μg/ml) | – | 3546 | 4239.79 | 62 | 2 | plasma exchange | 6239 | 9836.23 | 2.1 |
| M., 29 years old | f | 75 | 4.5 | 50 | 10.6 | finlepsin | 18 | 23 | 24 | 2 | – | 1322 | 379.43 | 2.55 |
| Ch.,32 years | f | 49 | 24 | unknown | – (paracetamol concentration upon admission 25.2 μg/ml) | barbiturates, chlorprothixene | 297.62 | 136.02 | 28 | 2 | – | 421.54 | 148.12 | 1.34 |
| I., 32 years | m | 58 | 15 | 44 | 8.13 | phenobarbital | 79.49 | 78.03 | 17 | 3 | – | 3238 | 1667 | 1.95 |

Notes: ALT — alanine aminotransferase, AST — aspartate aminotransferase, ACC — acetylcysteine, INR — international normalized ratio

*Table 4*

**Factors affecting the development of liver damage, duration of treatment in patients with paracetamol poisoning**

| Indicators | Group I (*n* =14) | Group II (*n* =6) | *P value* |
|---|---|---|---|
| Dose of paracetamol, g | 15.0 (7.5–20.0) | 20.0 (18.0–44.0) | 0.114 |
| Time between taking paracetamol and hospitalization, hours | 4.0 (2.63–9.5) | 12.5 (5.88–21.8) | 0.214 |
| Length of stay in the ICU, days | 2.5 (1.25–3.0) | 3.5 (2.0–5.0) | 0.289 |
| Total hospital stay, days | 4.0 (3.25–4.75) | 9.0 (8.25–9.75) | 0.044* |

Note: * - differences are statistically significant between the indicators ($p<0.05$). Data are presented as Me ($Q_1$–$Q_3$). ICU — intensive care unit

The median duration of hospitalization of all patients in the ICU was 2.5 (2.0–3.5) days, while in patients with hepatotoxic effect this indicator was 1.4-fold longer: (3.5 (2.0–5.0) versus 2.5 (1.25–3.0) days ($p$ = 0.289). The median length of hospital stay for patients with acute paracetamol poisoning was 4 (3.75–8.25) days. In a comparative assessment in patients with liver damage, this indicator was 2.25-fold higher (9.0 (8.25–9.75) versus 4.0 (3.25–4.75) days ($p$ = 0.044).

Statistical analysis showed that the dose of paracetamol in patients with the development of a hepatotoxic effect after paracetamol poisoning was 1.3-fold higher compared to patients in group I. The time before the start of ACC administration was 2.5-fold higher in patients with ALT levels over 50 U/l compared to patients whose ALT level was below the indicated values: 20.5 (11.0–28.0) versus 8.0 (7.5–17.0) hours ($p$ = 0.048) (Fig. 2).

A statistically significant increase in paracetamol index values by 5.4 times was revealed in patients with the development of a hepatotoxic effect compared with patients without this complication ($p$ = 0.032) (Fig. 3).

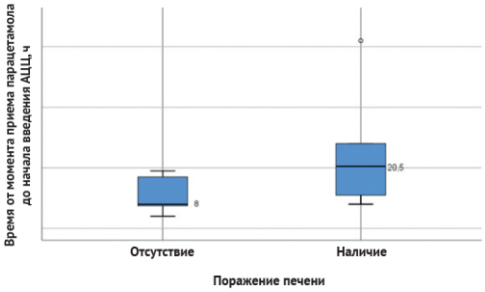


Fig. 2. Diagram of the time range between the moment of taking paracetamol and the initiation of ACC administration, depending on the presence of liver damage

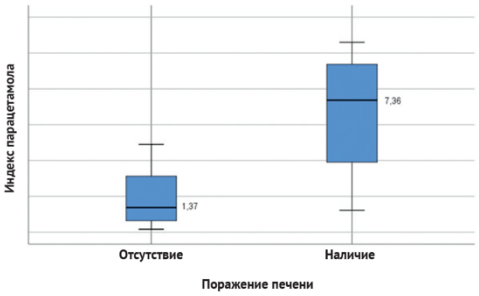


Fig. 3. Diagram of the range of paracetamol index value depending on the presence/absence of liver damage in case of paracetamol poisoning.

The development of hepatic encephalopathy, acute renal injury was not seen in any case. There were no indications for liver transplantation. In one case, a plasma exchange session was performed. All patients were discharged from the hospital in a satisfactory condition.

Correlation analysis showed that there was a moderate strength (a noticeable strength of the correlation according to Chaddock) tightness of the relationship between the increase in the level of ALT during the observation period and the paracetamol index ($r$ = 0.574, $p$ = 0.016), the increase in the level of ALT and the time before the start of the introduction of ACC ($r$ = 0.527, $p$ = 0.044). A weak correlation was determined between the increase in the content of ALT in the blood and age ($r$ = 0.326, $p$ = 0.161). The tightness of the relationship of medium strength was found between the paracetamol index and the time before the initiation of ACC administration ($r$ = 0.570, $p$ = 0.053).

## DISCUSSION

Paracetamol first appeared as an antipyretic and analgesic agent in the 1950s. The first case of paracetamol poisoning was documented in 1966 in Scotland. At that time, the pathophysiological mechanisms of liver damage associated with the toxic effects of the drug were unknown. In the 70s, with the help of experimental studies, scientists established the main pathways of paracetamol metabolism and the mechanism of toxic liver damage, as a result of which nomograms appeared that illustrate the dependence of the development of hepatotoxicity on the dose of the drug taken. Currently, despite the optimization of diagnostic methods to predict the development of liver damage and the improvement of treatment protocols, paracetamol poisoning is a serious problem in medicine, being the most common cause of acute liver failure worldwide [16, 17].

There is an opinion that gastric lavage is effective in the first hours after taking the drug by reducing the absorption of paracetamol [15]. So, according to Yu.V. Zobnin, this method should be used in the first 6 hours after taking the drug [16]. However, R. Hoffman et al. argue that gastric lavage is not advisable due to the high absorption rate of the drug and the presence of an effective antidote [6]. Our study showed that it is advisable to carry out gastric lavage in the early period, as evidenced by the values of the paracetamol index - 2.55 lower in patients who used this method.

According to a number of studies, activated charcoal should be used in the first 4 hours after taking paracetamol, as this helps to reduce the number of patients with serum paracetamol concentrations above the

critical level. In our study, we were unable to evaluate the effectiveness of activated charcoal in the first 4 hours after an overdose due to the small number of patients in this group. However, it should be noted that in 3 cases of early use of activated charcoal, the concentration of paracetamol in the blood exceeded the "treatment" line 1.86-, 3.3- and 6.6-fold.

Intestinal lavage was performed in all patients for the purpose of detoxification.

Already in the 70s in the USA it was established that ACC is an effective antidote for paracetamol poisoning. Since 1975, a 3-stage regimen for the intravenous administration of ACC has been used all over the world [17]:

Stage 1 — 150 mg/kg within 15 minutes (60 minutes);

Stage 2 — 50 mg / kg within4 hours;

Stage 3 — 100 mg / kg within 16 hours.

Currently, it is recommended to include ACC in the complex of treatment in case of a risk of liver damage, focusing on the dose, time of administration and concentration of paracetamol in the blood [6]. The indication for the introduction of ACC is the excess of the level of paracetamol in the blood above the "treatment line" according to the Rumack-Matthew nomogram. In our study, we used a nomogram 150 to predict the risk of liver damage. The values of this nomogram have been adopted in the paracetamol treatment guidelines in countries such as Canada, Australia, New Zealand, and the United States [18, 19]. In 2012, in the UK, the level of paracetamol serum concentration 4 hours after administration, at which the development of liver damage is possible, was reduced to 100 μg/ml [19]. Previously, this level of 100 was used only for the treatment of patients suffering from chronic alcohol intoxication, etc. In the absence of data on the exact time of administration and dose, an indication for antidote therapy is the presence of a serum paracetamol concentration of more than 10 μg/ml or clinical and laboratory signs of liver damage [6] .

There are various schemes for the introduction of ACC. However, the “classic” protocol in many countries is still the 3-stage scheme. Clinicians refuse oral administration of ACC and prefer intravenous administration, since the course of therapy is much shorter in this case (21 hours versus 72 hours), although it has been proven that the efficacy and safety of both routes of administration are the same [10]. The results of studies on the effectiveness of the use of high doses of ACC in a "massive" overdose of paracetamol are controversial [20, 21].

In recent years, a 12-hour protocol for intravenous administration of ACC in 2 stages has been widely used. The total dose of ACC according to the 2-stage regimen recommended in 2020 in Australia and New Zealand is similar to early protocols involving the administration of 300 mg/kg of ACC per day [18]. The results of a few clinical studies have shown that the effectiveness of the 21-hour and 12-hour protocols is the same, but the number of anaphylactic reactions is lower with a shorter course of ACC administration. According to available data, the use of the 12-hour regimen is accompanied by a reduction in the stay of patients in the ICU and hospital. In the UK, this method was included in the recommendations [9]. However, there was not enough justification for the introduction of a modified 12-hour scheme into world practice [10].

In our study, we used the standard 21-hour ACC administration regimen in 16 patients. The results obtained showed that in 37.5% of cases (n = 6) a hepatotoxic effect developed, while it should be noted that in 4 cases (22.2%) ALT and AST levels were initially elevated. In 2 patients (12.5%), despite the introduction of ACC, the development of liver damage was subsequently observed. It should be noted that their PI was 6.6 and 10.6, which indicates a high concentration of paracetamol in the blood. Previously, large clinical studies have shown that the use of ACC in the first 8 hours practically prevents the development of liver damage [6]. However, Cairney D.G. et al. found that in patients with elevated plasma paracetamol concentrations there was a risk of liver damage even with timely intravenous administration of ACC (in the first 8 hours) [22]. Angela L. et al. came to a similar conclusion [7, 8]. The authors of the study showed that a higher dose of ACC is needed when taking high doses of paracetamol (2-fold higher than the “treatment line” of the nomogram). The use of higher doses of ACC was associated with a significantly lower risk of hepatotoxicity [OR: 0.27 (95% CI: 0.08–0.94)]. The odds ratio was maintained when adjusted for the time of ACC and PI administration [7].

The analysis of our own data showed that the following factors had the greatest influence on the development of the hepatotoxic effect: the time from the moment of taking paracetamol to the administration of ACC, as well as the level of paracetamol in the blood. In patients with the development of liver damage, the time to antidote administration and the PI value were higher compared to group II patients than in the group of patients below the reference values by 2.5- and 5.4-fold, respectively ($p$ <0.05, statistically significant). This is consistent with the literature data [7, 8, 11].

## CONCLUSION

The obtained results indicate that the indication for the use of acetylcysteine in acute paracetamol poisoning is a high risk of liver damage. Its criteria are high doses of paracetamol, elevated levels of alanine aminotransferase and aspartate aminotransferase upon admission of patients to the hospital, and if it is possible to determine the concentration of paracetamol in the blood, an increase in the paracetamol index value of more than 1. The use of a 21-hour protocol for intravenous administration of acetylcysteine is effective in paracetamol poisoning and early its use in complex treatment almost always prevents the development of acute liver failure.

## FINDING

1. In 10 patients (62.5%) with a high risk of liver damage, who had a 21-hour regimen of acetylcysteine included in the complex of treatment, no hepatotoxic effect was detected.

2. The use of acetylcysteine according to a 21-hour protocol in patients with initially elevated levels of alanine aminotransferase and aspartate aminotransferase more than 50 U/l ($n$ = 4) (25%) provided a rapid positive change in laboratory and clinical parameters.

3. It was found that in 2 patients (12.5%), despite the introduction of acetylcysteine, due to the influence of concentration and time factors, liver damage developed. At the same time, the level of paracetamol in the blood was 6.6- and 10.6-fold higher, respectively, than the "treatment" line of the nomogram. The time from the moment of taking the drug to the start of the administration of acetylcysteine was 8 and 20 hours, respectively.

4. High-risk factors for the development of a hepatotoxic effect in case of paracetamol poisoning — the time range from the moment of taking the drug to the start of the administration of acetylcysteine is more than 8 hours and the value of the paracetamol index is more than 2.

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