ALGORITHM OF SUBSTRATE METABOLIC DRUGS ADMINISTRATION IN THE EARLY STAGE OF ACUTE ACETIC ACID POISONING

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ABSTRACT

Acute poisoning with acetic acid remains one of the most common types of chemical injuries. The article analyzes the use of metabolic drugs based on succinic acid in complex intensive therapy at an early stage of severe acetic acid poisonings. It is proved, that the use of these drugs significantly improves outcomes in patients with acute acetic acid poisoning by reducing the intensity of hemoglobinemia and also due to the antihypoxic, antioxidant and hepatoprotective properties of these medications.

Keywords: acetic acid, hemoglobinemia, metabolic medication, succinic acid, Cytoflavin, Succinasol, antihypoxic properties.

ARF – acute renal failure

$avDO_2$ – arteriovenous oxygen difference

CUO_2 – coefficient of oxygen utilization

LII – leukocyte index of intoxication

MM – middle molecules

NSI – neutrophils shift index

RECRC – the Republican Emergency Care Research Center

RITU – resuscitation and intensive therapy unit

VO_2 – oxygen consumption

INTRODUCTION

Acetic acid poisoning is one of the most common types of household poisoning not only in our country but also in the UIS countries [1–3]. This is due to the wide availability and the constant use of acetic acid in everyday life. Development of tissue hypoxia and activation of lipid peroxidation plays a great role in the pathogenesis of acetic acid poisoning, and therefore inclusion of drugs with antioxidant, antihypoxic and membrane-protective properties to the complex of therapeutic measures becomes appropriate [4-6].

In recent years, a number of metabolic substrate medications based on succinic acid have appeared. Such medications are highly effective in conditions of hypoxia and tissue ischemia [7]. Among this group of drugs complex substrate metabolic Cytoflavin and domestic product Succinasol have proved themselves in the intensive therapy of various diseases, including acute poisonings [7]. Cytoflavin is a balanced complex of two metabolites (succinic acid and riboxinum) and two coenzymes-vitamins: riboflavin-mononucleotide and nicotinamide [7].

Succinasol together with its Russian analogue Reamberin was developed on the base of succinic acid and a balanced set of salts. Calcium succsinasole contains magnesium (calcium antagonist) allowing the solution to have a complete ionic composition, which is especially important for patients in critical condition on the background of existing low concentration of magnesium in the blood plasma.

Antihypoxic effects of Cytoflavin and Succsinasol mostly result in the oxygen balance, which is manifested at the tissue level and confirmed by the growth of indicators such as oxygen consumption, coefficient of oxygen use and recycling, as well as an increase in arteriovenous oxygen difference [6, 7].

However, Cytoflavin and Succsinasol were not actively used in acetic acid poisoning. So, taking into account properties of those drugs, an algorithm of their use at an early stage of acute poisoning with acetic acid was developed in the Department of Toxicology, RECRC.

Objective: study of the effectiveness of metabolic drugs based on succinic acid at an early stage of severe acute poisoning with acetic acid.

MATERIAL AND METHODS

The object of the study was a group of 126 patients with severe acute acetic acid poisoning, treated at the Department of Toxicology Resuscitation, RECRC in 2010–2012. Patients were aged 17 to 54 years and arrived within a period of 1 to 3 hours after the poisoning. All patients were divided into three clinical groups according to the type of treatment.

Group I included 42 patients admitted in 2011-2012, who had been undergone a complex of traditional procedures (gastric lavage, antispasmodics, forced diuresis, alkalization of blood, hormone and heparin therapy) supplemented by infusion of substrate metabolic medication Cytoflavin. It was administered intravenously in the dose of 20.0 mL in 5% glucose solution, 2 times per 24h, starting on day 1–10 from admission of patients to the hospital.

Group II – 50 patients also admitted in 2011 - 2012. In this group, therapy included intravenous infusion of Succinasol 400 mL 2 times per 24h for 10 days.

Group III – 34 patients admitted in 2010 who underwent traditional comprehensive medical therapy.

Comparability of study groups was provided by: 1) exclusion of patients with severe somatic pathology (chronic cardiovascular and respiratory disorders, the pathology of the central nervous system) from research groups; 2) the lack of statistically significant differences between groups in age and severity of the condition.

Oxygen balance, partial O_2 and CO_2 tension in the arterial and venous blood, pH of arterial and venous blood were studied. Blood gases partial tension and blood pH were calculated using Medica EasyStat analyzer (Germany). Saturation (SaO_2) was studied using the NIHON KONDEM monitor setting. The design parameters of the oxygen transport system: oxygen consumption – VO_2; arteriovenous oxygen difference – $avDO_2$; coefficient of oxygen utilization – CUO_2 were calculated using the formula given in the monograph of G.A. Ryabov [8]. Examinations were carried out on admission, 6 hours later and on day 2.

The level of free hemoglobin in the blood was studied during the period of hospitalization – 6 and 12 hours after admission.

To assess the degree of hepato-renal failure, we measured the level of urea, creatinine, bilirubin, ALT, AST and diastase in serum (after knocking hemoglobinemia), as well as markers of endotoxemia – middle molecules (MM), leukocyte intoxication index (LII), neutrophils shift index (NSI) on the 3rd, 5th, 9th and 10th day.

Degree of the esophageal and stomach burn was determined by esophagogastroscopy on 1–2nd, 16–18th and 27th–30th days after poisoning. The incidence of pneumonia, acute renal failure (ARF), late esophagogastric bleeding, scarring stenosis of the esophagus and stomach, lethality were also studied.

Data processing was performed using Microsoft software and Excel-2003 spreadsheets. The criteria (lethality, incidence of complications) were rated by Oivin method of alternative variation.

RESULTS AND DISCUSSION

Initial state of all examined patients confirmed severe poisoning with acetic acid. The level of free hemoglobin on admission was 8.5 ± 2.2 g/L in patients of group I, 8.9 ± 3.3 g/L in group II and 8.1 ± 2.7 g/L in group III. In the dynamics on Cytoflavin therapy hemoglobinemia decreased by 68.2% 6 h later and by 84.1% 12 h later. Slightly higher detoxification effect was detected using Succinasol: hemoglobinemia decreased by 76.4%, and 12 h later it was almost completely controlled, being decreased by 92.6% (to 0.65 ± 0.28 g/L). In the comparison group dynamics of reducing free hemoglobin 6 and 12 h later was 52.8% and 74% respectively, lagging groups I and II 1.3–1.2 and 1.4–1.3 times respectively (Table 1).

Table 1

Dynamics of hemoglobinemia reduction in patients with acute acetic acid poisoning (n = 126)

Free hemoglobin, g/L	On admission	After 6 h	Δ %	After 12 h	Δ %
Group I (n=42)	8.5±2.2	2.7±1.18*	–68.2	1.35±0.25*	–84.1
Group II (n=50)	8.9±3.3	2.1±1.4	–76.4	0.65±0.28*	–92.6
Group III (n=34)	8.1±2.7	3.82±1.3	–52.8	2.1±0.87*	–74.1

Notes: * – $p < 0.05$. All values of Δ% and p – with respect to figures on admission

Violation of external respiration was observed in all examined patients upon arrival, and this fact was demonstrated by a decrease of oxygen consumption (VO_2), deterioration of tissue oxygen transport component (CUO_2) and arteriovenous difference of oxygen ($avDO_2$) (Table 2). There was an increase of VO_2 by 33.5%, CUO_2 by 47.2% and $avDO_2$ by 42.3% with statistically significant differences from the initial levels 12 hours after Cytoflavin infusion. In the group of patients treated by Succinasol, improving of VO_2, CUO_2 and $avDO_2$ was by 24.5%, 39.3% and 41.1%, which was slightly lower than in group I, but it was 1.1, 1.2 and 1, 3 times higher than in patients treated with conventional therapy, and this fact evidenced tissues oxygen uptake recovery (Table 2).

Table 2. Effect of succinic acid medications on the oxygen balance in acetic acid poisoning (n = 126)

Norm. index	Group I (n = 42)					Group II (n=50)					Group III (n=34)				
	On admission	After 12 h	Δ %	Day 2	Δ %	On admission	After 12 h	Δ %	Day 2	Δ %	On admission	After 12 h	Δ %	Day 2	Δ %
VO_2 (130 mL/min x m^2)	93.8 ±3.4	125.3 ±3.2*	+33.5	134.1 ±2.5*	+42.9	93.3 ±5.7	116.2 ±4.0*	+24.5	131.6 ±2.5*	+41	92.3 ±2.9	104.2 ±4.4*	+12.8	118.9 ±3.0*	+28.8
$avDO_2$ (40-60 mL/L)	31.2 ±1.7	44.4 ±2.3*	+42.3	51.3 ±2.1*	+64.4	32.1 ±1.2	42.6 ±2.4*	+32.7	45.3 ±2.6*	+41.1	32.8 ±2.3	38.2 ±2.8	+16.4	40.1 ±2.3	+22.2
CUO_2 (24-32%)	20.1 ±1.8	29.6 ±1.6*	+47.2	30.3 ±0.9*	+50.7	20.6 ±2.2	28.7 ±1.5*	+39.3	29.1 ±0.9*	+41.2	21.4 ±1.8	19.3 ±1.8	–9.8	20.5 ±1.7	–6.5

Notes: * – $p < 0.05$. All values of Δ% and p – with respect to figures on admission; VO_2 – oxygen consumption;

$avDO_2$ – arteriovenous oxygen difference; CUO_2 – the coefficient of oxygen utilization

Table 3. Cytoflavin influence on blood biochemical indices in acetic acid poisoning (n = 126)

Norm. index	Group I (n=42)					Group II (n=50)					Group III (n=34)				
	Day 3	Day 5	Δ %	Day 9-10	Δ %	Day 3	Day 5	Δ %	Day 9-10	Δ %	Day 3	Day 5	Δ %	Day 9-10	Δ %
Urea (2.5-8.3 mmol/L)	17.6± 1.1	12.9± 0.02*	–26.7	9.55 ± 0.01 *	–45.7	16.1± 1.4	8.26± 0.02*	–48.6	8,27 ± 0,01 *	–48.6	19.4± 2.1*	17.3± 0.05	– 10.8	11,5 ±0,7 *	–40,7
Creatinine (0.088-0.19 mmol/L)	0.26± 0.01	0.23± 0.01*	–11.5	0.14 ± 0.02 *	–46.1	0.28± 0.01	0.18± 0.01*	–35.6	0	–57.1	0.31± 0.07*	0.29± 0.05	–6.4	0.21 ± 0.05	-32.2
ALT (0-42 u/L)	155.2 ±9.4	126.6± 9.3*	–18.4	62.3 ±6.6 *	–59.8	142.4± 11.1	63.7± 2.9*	–55.2	28.1 ±0.5 *	–80.2	182.8 ±22.8 *	164.6± 11.5	–9.7	93.9 ±7.8 *	–48.4
AST (0–37 u/L)	79.0± 0.5	44.9± 0.5*	–43.1	31.2 ±0,5 *	–60.5	76.6± 0.5	39.2± 1.4*	–48.8	20.2 ±2.9 *	–73.6	121.0 ±9.2	108.8± 8.1	-10.8	69.2 ±7.7 *	–42.8
Diastase of blood (16-32 mg/mL x hr)	76.6± 4.09	62.4± 4.1*	–18.53	49.7 ±3.1 *	–35.1	79.0± 3.4	34.7± 5.6*	–56.0	21.2 ±2.2 *	–73.1	112± 6.3	106.4± 7.5	–5	78.7 ±6.2 *	–29.7
Total bilirubin (8.55-20.5 mmol/L)	38.8± 2.2	29.2± 3.4	–24.7	20.9 ±2.4 *	–46.1	39.1± 2.6	16.0± 1.9*	–59.0	14.4 ±2.1 *	–63.1	43.2± 4.9	33.2± 2.9	-23.1	26.3 ±2.5 *	–39.1

Notes: * – p <0.05. All values of Δ% and p – with respect to the primary figures taken on day 3 (after elimination of hemoglobinemia)

Table 4. Cytoflavin influence on endotoxemia dynamics in acetic acid poisoning (n = 126)

Norm. index	Group I (n = 42)					Group II (n=50)					Group III (n=34)				
	Day 3	Day 5	Δ %	Day 9-10	Δ %	Day 3	Day 5	Δ %	Day 9-10	Δ %	Day 3	Day 5	Δ %	Day 9-10	Δ %
MM (0.23± 0.02 optical density units)	0.52 ±0.24	0.266 ±0.32	–48.8	0.184 ±0.48*	-64.6	0.588 ±0.14	0.324 ±0,12	-44.8	0.285 ±0.48*	–51.5	0.69 ± 0.03	0.56 ± 0.14	-23.2	0.46 ± 0.01 *	–33,3
LII (1.0± 0.5 units)	5.72 ±1.02	4.06 ±0.85*	–29.0 1.9 ±0.93*	–66.7	5.38 ± 1.05	5.12 ±0.16	–4.8	2.8 ± 0.33 *	–47.5	5.61 ±0.92	5.72 ± 1.17	+1.9	4.3± 0.74	-23.3	
NSI (0.06 units)	0.28 ±0.05	0.20 ±0.05	–28.5	0.11 ±0.04*	-60.7	0.32 ±0.03	0.24 ±0,07	-25.0	0.19 ±0.08	–40.6	0.31 ± 0.05	0.32 ± 0.05	+3.2	0.29 ± 0.11	–6.4

Notes: * – p <0.05. All values of Δ% p – with respect to the primary figures taken on day 3 (after elimination of hemoglobinemia); MM – middle molecules; LII – leukocyte index of intoxication; NSI – neutrophils shift index.

Oxygen balance remained low on day 2 in the comparison group, whereas in groups I and II it became closer to normal levels (Table 2).

Changes of blood biochemical indices showed that the best detoxification effect was observed in patients of group II receiving Succinasol. Such effect was proved by a decrease of ALT on day 5 and on day 9–10 by 55.2% and 80.2% respectively, AST – by 48.8% and 73.6%; bilirubin – by 59% and 63.1%; diastase – by 56% and 73.1%; urea – by 48.6% and 48.6%; creatinine – by 35.6% and 57.1%. Actually, normalization of these levels occurred. In group I (patients treated by Cytoflavin) detoxification effect was somewhat lower than in the group treated by Succinasol, but in group III changes of biochemical indices reduction stayed considerably behind the groups I and II, and also ALT, AST, bilirubin, diastase, urea and creatinine remained high on day 9– 0 (Table 3).

Treatment effect on laboratory indices of endotoxemia is given in Table 4.

As seen from Table 4, in group I the level of blood MM (fraction E254) decreased already on day 5 by 48.8% from initial data, it was 1.3 times lower than in group II s and 1.7 times lower than in group III. On day 9–10 the group I showed a decrease of MM by 64.6% from

the initial level, so the concentration of MM decreased to its normal level of 0.184 ± 0.48. We have found that when using Succinasol in group II patients less evident changes in the elimination of MM were observed, but even in this group the concentration of MM in the blood on day 9–10 was only slightly higher than the normal level – 0.285 ± 0.48. It should be noted that reduction of MM in the comparison group III was only 33% on day 9–10 and was 2.3 times lower than the results of group I, and 1.5 times lower than in group II. Given pro-oxidant properties of the MM [9] this fact was an indirect evidence of the antioxidant activity of Cytoflavin and Succinasol.

As seen from Table. 4, with respect to LII the most distinct effect was observed in patients of group I treated by Cytoflavin: on day 5 and day 9–10 LII reduction change was 29% and 66.7%, so the level of LII was 1.3–1.5 times lower than that in group II and 1.4–2.3 times lower than in the group III respectively.

NSI reduction was also the most prominent in group I patients. On day 5 and day 9–10 when Cytoflavin started to be used, NSI values were 28.5% and 60.7% below the initial level, thereby 1.2–1.7 times less than in group II and 1.6–2.6 times less than in the comparison group respectively.

Significant improvement was seen in patients' condition at the end of Cytoflavin and Succinasol infusion: pain intensity decreased; there was a feeling of "freedom of breathing." Objectively, the improvement was normalized skin color, dyspnoea and tachycardia reduction, as well as the normalization of blood pressure.

Analysis of succinic acid drugs effectiveness criteria showed that the incidence of pneumonia was the lowest in group I – 21.4%, followed by group II – 28%, and in the comparison group III pneumonia developed in 52.9% of patients, i.e. in group III, it occurred 2.5 and 1.8 times higher than in groups I and II, respectively. In contrast, ARF developed less frequently in patients treated by Succinasol – 6%, followed by group I – 9.52%. In group III this figure was 29.4%, which was 3.0 and 4.9 times higher than in groups I and II, respectively. In group I, there were 2 deaths (4.7%), the average duration of treatment was 17,8 ± 2,4 days. In group II, 4 patients died (8%), and duration of treatment was 19,3 ± 2,1 days. In the comparison group III, 8 patients died (23.5%), and the average hospital stay was within 25 ± 2,2 days, being 1.3 and 1.2 times higher than in groups I and II (Table 5).

Table 5. Clinical criteria for the intensive therapy efficacy in patients with acetic acid poisoning (n = 126)

Groups	The incidence of pneumonia		The incidence of ARF		Number of patients died		Length of stay in RICU
	abs	%	abs	%	abs	%	
Group III (n = 34)	18	52.9	10	29.4	8	23.5	25±2.2
Group II (n = 50)	12	28*	3	6*	4	8**	19.3±2.1**
Group I (n = 42)	9	21.4*	4	9.5*	2	4.7*	17.8±2.4*

Notes: * – $p < 0.05$; ** – $0.05 < p < 0.1$. All comparisons are calculated with respect to the comparison group (group III) data; statistical analysis of the lethality frequency differences and late complications is made using an alternative method of variation; ARF – acute renal failure; RICU – resuscitation and intensive care unit.

In general, as seen from the results of statistical processing of the material, changes in clinical laboratory values in the phases of research of groups I and II patients in most cases are statistically significant but that is not observed in group III. This is a compelling objective evidence of the effectiveness of metabolic drugs used.

CONCLUSION

1. In severe poisoning with acetic acid there are fatal metabolic disorders associated with hyper lipid peroxidation and accompanied by the development of tissue hypoxia and endogenous intoxication syndrome.

2. Cytoflavin and Succinasol significantly increase the effectiveness of treatment of patients with acute acetic acid poisoning by reducing the intensity of blood hemolysis, recovery of tissue respiration, and due to the antioxidant and hepatoprotective properties of the drugs. In addition, Cytoflavin is more antihypoxic than Succinasol, and less detoxicative.

3. These data allow us to recommend infusion of Succinasol as detoxification solution in acute acetic acid poisoning in case of toxic hepatitis and nephropathy development. Cytoflavin infusion is preferred when there is a prevalence of tissue hypoxia and endotoxemia signs.

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