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Influence of Cytisine Derivatives and Succinic Acid Combination on Acute Alcohol and Hypnotic Drug Intoxication in Rats

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Abstract

Succinic acid (SA) containing remedies belong to drugs of a metabolic type of action, the pharmacotherapeutic effects of which are aimed at restoring biochemical metabolic reactions disturbed by pathological processes. Alcoholic coma is often accompanied by respiratory failure. The purpose of this work is to study the effect of combinations of cytisine, N-methylcytisine and benzylcytisine with succinic acid in a ratio of 1:1 on the acute alcohol poisoning. The studied compositions have an antitoxic effect in moderate alcohol poisoning. Thus, SA 10 mg/kg reduces the duration of narcotic sleep by 40%, cytisine at a dose of 0.1 mg/kg - by 66.6%, and the composition "cytisine:SA" - by 74.6%. Compositions "N-methylcytisine:SA" and "N-benzylcytisine:SA" at a dose of 0.1 mg/kg - by 35.2 and 41.3%, respectively, yielding to cytisine, SA and their composition, but showing a significant reduction in the narcotic sleep duration.

Keywords: *acute alcohol intoxication, cytisine derivatives, jasmonic acid, antitoxic*

INTRODUCTION

Ethanol toxicity can occur in both acute and chronic settings, representing two different spectra of disease. Acute ethanol intoxication usually follows the ingestion of a large amount of alcohol and is a clinically harmful condition (World Health Organization: Global Status Report on Alcohol and Health 2014)[11].

Alcohol use disorder (AUD) is responsive to psychosocial treatments, including cognitive-behavioral therapy and motivational enhancement therapy. Alcohol affects multiple neurotransmitter systems, and thus pharmacotherapy for AUD is also effective. The three medications approved to treat AUD—disulfiram, naltrexone (oral and long-acting injectable formulations), and acamprosate—are underprescribed, despite being considered first-line treatments in clinical practice guidelines (Makara N. S et.al. 2015)[6] . AUD is commonly accompanied by a variety of psychiatric disorders (e.g., drug use disorders, major depression, bipolar disorder, and antisocial personality disorder), medical problems (e.g., alcohol withdrawal, liver disease, pancreatitis, and cancer of the head, neck, liver, colon, or rectum),

andpsychosocial problems (e.g., accidental injuries, aggression, violence, and suicide) (Azamatov A.A et.al 2013., Rehm J et.al 2014., Livne O et.al. 2022)[2,5,8].

Medications containing succinic acid belong to metabolic-type drugs whose pharmacotherapeutic effects are aimed at restoring biochemical metabolic reactions disrupted by pathological processes. Medications of this type of action are widely used in cardiology, neurology, and hepatology, since disruptions of biochemical processes in the myocardium, nervous tissue, and liver are observed more frequently than in other organs and systems of the body. The antihypoxic effect of succinic acid (SA) is based not only on its ability to activate the succinate dehydrogenase pathway of ATP resynthesis in the ischemic zone, reduce the level of NAD-dependent Krebs cycle substrates and fatty acids, but is also associated with stimulation of cytochrome oxidase activity, which is a key enzyme of the mitochondrial respiratory chain in cells. Succinate-containing medications, for example, Reamberin, reduce the time patients spend in a comatose state and decrease mortality in cases of neurotoxic poisoning. It is known that succinic acid (SA) is used to reduce the negative effects of alcohol consumption, and Reamberin is used in the treatment of acute alcohol intoxication and in managing withdrawal syndrome (Zakharov V.V et.al. 2004., Rumyantseva S. A et.al. 2006)[12,9].

Alcoholic coma is often accompanied by respiratory disturbance. We previously established that N-(3,4-methylenedioxybenzyl) cytisine hydrochloride has a pronounced antitoxic effect in acute alcohol intoxication, and N-(3,4-methylenedioxybenzyl) cytisine hydrochloride is 2.8 times less toxic than cytisine (Henry R et.al)[3].

The aim of this work is to study the effects of combinations of cytisine, N-methylcytisine and benzylcytisine with succinic acid in a 1:1 ratio on the course of acute alcohol and hypnotic drug poisoning.

MATERIALS AND METHODS.

Cytisine and its derivatives were provided by the Laboratory of Alkaloid Chemistry at the Institute of the Chemistry of Plant Substances, Academy of Sciences of the Republic of Uzbekistan.

The substances were administered subcutaneously to white mice 10-15 minutes before the intraperitoneal administration of 24% ethanol at a dose of 4.8 g/kg. The effect of the substances was assessed by the duration of lateral position (narcotic sleep) in the animals.

RESULTS AND DISCUSSION

The obtained results are presented in the table, which shows that the studied compositions in a 1:1 ratio possess antitoxic effects in moderate alcohol poisoning. Thus, SA (succinic acid) at 10 mg/kg reduces the duration of narcotic sleep by 40%, cytisine at a dose of 0.1 mg/kg - by 66.6%, and the "cytisine:SA" composition - by 74.6%. The compositions "N-methylcytisine:SA" and "N-benzylcytisine:SA" at a dose of 0.1 mg/kg reduced the duration by 35.2% and 41.3%, respectively, being less effective than cytisine, SA and their composition, but still showing a significant reduction in the duration of narcotic sleep.

Table

The effect of combinations of cytisine and its derivatives with SA on acute alcohol intoxication in mice (n=10)

№	Group	Dose, mg/kg	Duration		Efficacy, %
			min.	%	
1	Control (ethyl alcohol)	4.8	107.6±4.2	100%	-
2	Succinic acid	5.0	72.4±2.8	67.2	32.8
		10.0	64.5±3.1	59.9	**40.1**
3	Cytisine	0.1	36.1±2.4	33.5	**66.5***
		0.5	37.3±2.7	34.6	65.4*
		1.0	40.2±2.5	37.3	62.7*
		5.0	59.3±3.6	55.1	44.9
4	Cytisine:SA (1:1)	0.1	27.4±4.2	25.4	**74.6***
		0.5	29.6±3.4	27.5	**72.5***
		1.0	44.8±2.9	41.6	58.4
		2.0	51.0±3.6	47.3	52.7
		5.0	62.5±4.0	58.0	42.0
	N-methylcytisine:SA (1:1)	0.1	69.8±3.8	64.8	**35.2***

5		0.5	71.2±4.0	66.1	33.9
		1.0	76.4±2.5	71.0	29.0
		2.0	80.2±3.6	74.5	25.5
		5.0	86.5±4.3	80.3	19.7
6	N-benzylcytisine:SA (1:1)	0.1	63.2±2.7	58.7	**41.3***
		0.5	68.4±3.6	63.5	36.5
		1.0	71.2±4.1	66.1	33.9
		2.0	76.5±3.7	71.0	29.0
		5.0	82.4±2.9	76.5	23.5

Note: *P=0.05 compared to the control group

The study of the combination's effect on acute urethane intoxication showed that this combination exhibits antidotal action at a dose of 2.0 mg/kg intraperitoneally, while the peak action of succinic acid is at 100.0 mg/kg (table 2).

Table 2 Effects of combinations of cytisine and its derivatives with succinic acid (1:1) on the narcotic action of urethane in mice with subcutaneous administration (n=6)

№	Experimental conditions	Dose, mg/kg	Duration		Efficacy, %
			min.	%	
1	Control urethane 1300 mg/kg i.p. (intraperitoneal administration)	1300.0	93.5±3.8	100%	-
2	Succinic acid s.c. (subcutaneous administration) after 30 min Urethane 1300.0 mg/kg i.p.	25.0	49.3±2.7	52.7	47.3*
		50.0	46.5±2.3	49.7	50.3*
		100.0	45.2±2.2	48.3	51.7*
3	Cytisine s.c. after 30 min. Urethane 1300.0 mg/kg i.p.	0.1	31.3±2.6	33.4	66.6*
		0.5	36.1±2.9	38.6	61.4*
		1.0	40.0±3.1	42.7	57.3*
		2.0	52.9±2.8	56.5	43.5*
4	Cytisine:SA s.c. after 30 min. Urethane 1300.0 mg/kg i.p.	0.1	67.0±3.3	30.8	69.2*
		0.5	30.3±3.5	32.5	67.5*
		1.0	38.1±3.0	41.9	58.1*
		2.0	52.7±3.6	56.4	43.6*
5	N-methylcytisine:SA s.c. after 30 min. Urethane 1300.0 mg/kg i.p.	0.1	45.4±3.5	48.5	51.5*
		0.5	41.8±3.4	44.7	55.3*
		1.0	47.1±3.2	50.3	49.7*
		2.0	59.6±3.6	63.7	36.3
6	N-benzylcytisine:SA s.c. after 30 min. Urethane 1300.0 mg/kg i.p.	0.1	11.7±2.7	12.7	87.3*
		0.5	17.2±3.5	18.5	81.5*
		1.0	21.8±2.8	23.3	76.7*
		2.0	40.1±2.6	42.8	57.2*

Note: *P=0.05 compared to the control group

The study of the combination's effect on acute sodium ethaminal intoxication showed that this combination exhibits antidotal action at a dose of 2.0 mg/kg subcutaneously, while the peak action of succinic acid is at 100.0 mg/kg (table 3).

Table 3 Effects of combinations of cytisine and its derivatives with succinic acid (1:1) on the narcotic action of sodium ethaminal in mice with subcutaneous administration (n=6)

№	Experimental conditions	Dose, mg/kg	Duration		Efficacy, %
			min.	%	

1	Control Sodium ethaminal 50.0 mg/kg i.p.	50.0	123.8±4.2	100%	-
2	Succinic acid s.c. after 30 min. Sodium ethaminal 50.0 mg/kg i.p.	25.0	62.3±2.8	50.3	49.7
		50.0	59.2±3.1	47.8	52.2*
		100.0	55.4±2.5	44.7	55.3*
3	Cytisine s.c. after 30 min. Sodium ethaminal 50.0 mg/kg i.p.	0.1	40.6±2.2	32.7	67.3*
		0.5	44.9±2.6	36.2	63.8*
		1.0	56.5±3.2	45.6	54.4*
		2.0	71.0±3.4	57.3	42.7*
4	Cytisine:SA s.c. after 30 min. Sodium ethaminal 50.0 mg/kg i.p.	0.1	32.9±3.5	27.3	72.7*
		0.5	36.8±3.8	30.5	69.5*
		1.0	53.4±3.2	43.1	56.9*
		2.0	59.7±2.9	48.2	51.8*
5	N-methylcytisine:SA s.c. after 30 min. Sodium ethaminal 50.0 mg/kg i.p.	0.1	51.6±2.9	41.6	58.4*
		0.5	35.1±2.5	28.3	71.7*
		1.0	44.0±2.2	35.5	64.5*
		2.0	70.8±2.8	57.1	42.9*
6	N-benzylcytisine:SA s.c. after 30 min. Sodium ethaminal 50.0 mg/kg i.p.	0.1	18.9±2.1	15.2	84.8*
		0.5	25.7±2.5	20.7	79.3*
		1.0	32.8±2.7	26.4	73.6*
		2.0	40.7±2.1	32.8	67.2*

Note: *P=0.05 compared to the control group

In recent years, studies have emerged on the use of succinic acid salts as a substrate antihypoxant. Succinic acid reduces the degree of post-hypoxic metabolic acidosis of various origins and activates the anaerobic production of high-energy compounds against the background of oxygen deficiency (Vonghia L et.al. 2008)[10]. The advantages of succinic acid are most prominently manifested under conditions of cytotoxic hypoxia, when NAD-dependent electron transport in the respiratory chain is inhibited, while SDH activity and endogenous succinate production increase (Azamatov A.A et.al. 2020)[1]. Previously, we demonstrated that N-benzylcytisine at a dose of 1 mg/kg (subcutaneously) exhibits pronounced antihypoxic effects in models of normobaric hypoxia with hypercapnia, hemic hypoxia, and cytotoxic hypoxia, increasing the survival time reserve of animals by 43%, 47%, and 48.5%, respectively (Livanov G.A et.al 2001)[4]. In contrast, cytisine does not exhibit antihypoxic effects (Polyakov I. A et al. 2009)[7].

Conclusion. In conclusion, the conducted studies have established that the investigated compositions of succinic acid with cytisine derivatives demonstrate antidotal activity against acute alcohol and hypnotic drug intoxication Therefore, further investigation of the protective efficacy and mechanism of action of these compounds in pathological conditions caused by alcohol and drugs is warranted.

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