TREATMENT OF EXPERIMENTAL METABOLIC ALKALOSIS WITH SORBAMINE

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Clinical observations have shown that some pathological processes are accompanied by a marked shift of the acid–base balance of the blood (ABB) toward alkalosis which, like acidosis, may greatly aggravate the course of the disease and worsen the prognosis [1, 2, 3]. Metabolic alkalosis is expressed as an uncompensated shift of the blood pH and an increase in the concentration of standard bicarbonate (SB) and base excess (BE).

To combat metabolic alkalosis in clinical practice various infusion media liberating H^+ ions *in vivo* (solutions of ammonium chloride, of hydrochlorides of amino acids, and hydrochloric acid) or restoring the normal electrolyte balance (potassium chloride solution) are currently used. However, none of these media can satisfy the main demand made on solutions for intravenous injection, namely a combination of high effectiveness with complete safety for the recipient [6-8, 11].

Considering the shortcomings of existing methods of treatment of alkalosis, a new infusion solution, more physiological in its action and composition, has been developed in the Central Research Institute of Hematology and Blood Transfusion, Ministry of Health of the USSR, on the basis of amino acids in hydrochloride form, with the name of sorbamine.

Individual amino acids have been used previously in the form of their hydrochlorides to correct alkalosis. For instance, solutions of arginine hydrochloride or lysine hydrochloride have been found to be quite effective, as reported in both experimental and clinical publications [5, 9, 12].

However, if large quantities of one amino acid are injected, there is a real possibility of disturbance of the normal ratio between amino acids in the blood. In this new preparation, the necessary quantity of acid valencies was shared among three amino acids in the form of their hydrochlorides, which are produced by industry. The ratio by weight of arginine-HCl, histidine-HCl, and lysine-HCl, composing the solution, was thus chosen on the basis of their physiological ratio in human blood (1:1:1.8). The solution also includes potassium chloride to compensate the hypokaliemia which accompanies alkalosis, and sorbitol, to facilitate fixation of potassium by the cells and to stimulate diuresis.

Sorbamine has the following formula: L-arginine-HCl 19 g, L-histidine-HCl 19.3 g, L-lysine-HCl 33.5 g, potassium chloride 2.6 g, D-sorbitol 30 g, water for injection to 1 liter. The theoretically calculated content of H^+ ions in the solution is 365 meq/liter and the pH of the solution varies from 5.2 to 6.0.*

EXPERIMENTAL METHOD

The therapeutic effectiveness of sorbamine was studied in experiments on 39 cats anesthetized with pentobarbital (30 mg/kg), on a model of metabolic alkalosis, induced by the

*An application (No. 3298089) has been made to patent the composition of sorbamine, with priority from March 5, 1981.

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TABLE 1. Principal Parameters of ABB of Arterial Blood and Plasma Potassium Concentration in Metabolic Alkalosis (M ± m)

Period of investigation	pH	pCO_2, mm Hg	BE, meq/liter	Standard bicarbonate, meq/liter	Potassium concentration, meq/liter
Initial data (14)	7,32±0,02	32,0±3,1	—8,8±0,9	17,5±0,6	3,83±0,1
After infusion of 4% solution of sodium bicarbonate in a dose of 9 ml/kg body weight					
after 30 min (14)	7,45±0,02*	34,3±4,8	—1,5±0,9*	21,0±1,7*	—
after 2 h (11)	7,45±0,03*	35,2±9,0	—2,4±1,2*	22,1±1,0*	
after 3 h (5)	7,42±0,04*	31,1±4,1	—3,1±1,3*	21,5±1,0	3,5±0,1*

Legend. Here and in Tables 2 and 3, asterisk indicates $P < 0.05$ compared with initial data. Number of tests in parentheses.

TABLE 2. Principal Parameters of ABB of Arterial Blood and Plasma Potassium Concentration during Treatment of Moderately Severe Metabolic Alkalosis by Sorbamine (M ± m)

Period of investigation	pH	pCO_2, mm Hg	BE, meq/liter	Standard bicarbonate, meq/liter	Potassium concentration, meq/liter
Initial data (19)	7,38±0,01	30,2±1,3	—6,1±0,6	19,4±0,4	4,2±0,1
30 min after infusion of 4% solution of sodium bicarbonate in a dose of 9 ml/kg body weight (19)	4,47±0,01*	31,2±1,3	—0,5±0,8*	24,3±0,6*	—
After infusion of sorbamine:					
1 h (19)	7,42±0,01*	27,1±1,1	—4,9±0,5*	20,3±0,4*	—
3 h (19)	7,41±0,01*	27,0±0,01	—5,4±0,5	19,9±0,4	4,1±0,2
24 h (17)	7,39±0,01	27,2±1,9	—6,3±0,8	19,1±0,5	4,5±0,3

TABLE 3. Principal Parameters of ABB of Arterial Blood during Treatment of Severe Metabolic Alkalosis by Sorbamine (M ± m)

Period of investigation	pH	pCO_2, mm Hg	BE, meq/liter	Standard bicarbonate, meq/liter
Initial data (6)	7,38±0,02	32,2±1,8	—3,4±1,3	21,2±1,1
30 min after infusion of 4% solution of sodium bicarbonate in a dose of 18 ml/kg body weight (6)	7,57±0,02*	35,2±3,1	—10,5±2,0*	33,1±1,7*
After infusion of sorbamine:				
1 h (6)	7,45±0,04	34,2±3,2	—0,01±2,0	24,0±1,7
3 h (6)	7,39±0,02	32,8±1,8	—4,2±1,1	20,5±0,8
24 h (6)	7,39±0,01	32,2±1,6	—3,4±1,1	21,1±0,9

method described previously [4], by intravenous injection of sodium bicarbonate solution in a dose of 4.3 meq base/kg body weight (9 ml/kg of a 4% solution) and 8.6 meq base/kg body weight (18 ml/kg of a 4% solution).

There were three series of experiments: series I) control experiments without correction of the alkalosis (14 animals), series II) experiments with correction of moderately severe alkalosis (19 animals), series III) experiments with correction of severe alkalosis (six animals).

In series II and III infusion of sorbamine by intravenous drip began 30 min after infusion of sodium bicarbonate, against the background of developed metabolic acidosis. The dose of solution (V) was calculated individually depending on the shift of BE after injection of sodium bicarbonate by the formula:

$$V = \frac{0.3 \cdot a \cdot 1000}{365} \text{ ml/kg},$$

where a is the difference between values of BE in the initial state and after injection of sodium bicarbonate solution (in meq/liter), 0.3 stands for the quantity of H^+ ions (in meq/kg body weight) required to reduce the base excess (BE) in the blood by 1 meq/liter [10], and 365 is the content of H^+ ions in 1 liter of sorbamine.

The following parameters were studied in the experiments: the survival rate of the animals during 3 days after the experiment, the blood pressure (BP) in the femoral artery, values of ABB in arterial blood taken anaerobically, using a micro-Astrup apparatus, and the potassium concentration in the blood plasma (in experiments of series I and II) by flame photometry. The numerical results were subjected to statistical analysis by the difference method.

EXPERIMENTAL RESULTS

The blood ABB of cats in the initial state was characterized by lower actual pH, lower SB concentration, and smaller BE than ABB of human blood (Table 1).

Injection of a 4% solution of sodium bicarbonate in a dose of 9 ml/kg body weight led to the development of persistent metabolic alkalosis and hypokaliemia. Metabolic alkalosis was characterized by changes not only in ABB. In most animals, for instance, BP fell 3 h after infusion of sodium bicarbonate to 80-90 mm Hg compared with 130-140 mm Hg in the initial state, and the respiration rate increased.

The severity of the induced alkalosis also was reflected in high mortality among animals in the experiments of series I: 13 of the 14 cats died within 3 days after the experiment. During the first 24 h, eight cats died, seven of them 3-4 h after injection of sodium bicarbonate, and five cats which were in a state of coma throughout died on the 2nd-3rd day after the experiment.

In the experiments of series II complete compensation of the shift toward alkalosis was observed 3 h after infusion of sorbamine with respect to the principal metabolic parameters of ABB (BE and SB). After 24 h all parameters of ABB, including pH, had returned to their initial level (Table 2).

Normalization of ABB was accompanied by stabilization of BP and respiration and by correction of the hypokaliemia. The mortality of the animals was significantly reduced: Two of 19 cats died.

The results of the experiments of series III, in which severe alkalosis was produced by injection of a double dose of the bases compared with the control and the previous series, are particularly interesting. In this case also, however, the alkalosis was successfully compensated and all the animals survived (Table 3).

A series of experiments also was devoted to the study of harmlessness of the solution for the animal, which showed that sorbamine has neither acute nor chronic toxicity and affects neither the function nor the morphology of the organs and systems of the body.

Sorbamine can thus be recommended for clinical study in patients with metabolic alkalosis. The preparation has been approved by the Pharmacologic Committee of the Ministry of Health of the USSR for clinical trials (Protocol No. 16 dated July 10, 1981).

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