EFFECT OF INTRAVENOUS INJECTIONS OF PROCAINE ON OUTCOME OF THE POSTHEMORRHAGIC REACTION

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Experiments on 48 dogs and 50 rabbits showed that intravenous injections of procaine at various times of the response to acute massive blood loss increase the chance of survival and the life span of the animals. Procaine injections increase the rate of blood flow and the stroke and minute volume of the heart and, as a whole, they prevent the onset of the late period of hemorrhagic shock. It is concluded that intravenous procaine injections delay the development of the pathological process and thus enable a more complete mobilization of compensatory reactions.

KEY WORDS: massive blood loss; procaine; survival.

Irreversible changes after acute massive blood loss have been shown to develop more rapidly than compensatory reactions can be mobilized [6, 14, 19], so that death frequently takes place before the body has succeeded in fully using all its resources [4, 20]. An urgent task in therapeutics is thus to delay the development of the pathological process. Considering the nature of the pharmacological action of intravenous procaine and its relatively wide application in clinical medicine for the treatment of seriously ill patients [3, 7, 9, 17], it seemed that this agent ought to have a significant effect on the outcome of the posthemorrhagic reaction.

The object of this investigation was to discover whether intravenous procaine injections would delay the course of the pathological process following acute massive blood loss.

EXPERIMENTAL METHOD

Experiments were carried out on 48 dogs and 50 rabbits. Bleeding was carried out in one stage from the femoral artery of the dogs and the common carotid artery of the rabbits until the blood pressure fell to 40-45 mm Hg. Throughout the experiment the blood pressure in these vessels, the pulse and respiration rates, the central venous pressure (a polyethylene catheter was introduced through the femoral vein as far as the orifice of the posterior vena cava in the dogs and through the external jugular vein to the orifice of the anterior vena cava in the rabbits), the temperature in the rectum and muscles (with a "Biotherm" electrothermometer), the EEG (unipolar recording by needle electrodes from the parietal regions), the ECG (standard lead II), and the EMG (bipolar recording with needle electrodes from the posterior cervical muscles of the dogs and the biceps femoris muscles of the rabbits) were recorded on the 4ÉÉG-1 electroencephalograph. Changes in spontaneous activity and changes evoked by photic (10 flashes per second) and acoustic (2000 Hz) stimulation were analyzed. At vital stages of the experiments photographs were taken of the vessels of the rabbits' optic fundi (with a large nonreflecting ophthalmoscope and the "Zenit" camera) and conjunctival vessels of the dogs (MBS-2 microscope and "Zenit" camera). Changes in the conjunctival vessels were estimated quantitatively by comparison with a photograph of the objective micrometer or ocular scale. The scale for the vessels of the optic fundus was the initial caliber of the retinal arteries (taken as unity). Other parameters investigated included the circulating blood volume (by the dye dilution method with T-1824), the hematocrit number, the hemoglobin concentration and erythrocyte count, the blood flow velocity

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TABLE 1. Changes in Some Indices in Dogs under the Influence of Intravenous Procaine Injections after Acute Massive Blood Loss (M ± m)

Series of experiments	Arterial pressure (in mm Hg)	Central venous pressure (in mm water)	Pulse rate (beats/min)	Circulating blood volume (in ml/kg)	Circulating plasma volume (in ml/kg)	Lobeline time time (sec)	Systolic index (in ml/m^2)	Cardiac index (in liters/m^2·min)	Conjunctival vessels (in μ)	
									arteries	veins
I. Control: Initial values	121±2	+35±4	66±2	78±1,3	38±2	18±1	23±0,4	1,52±0,3	25	50
phase of inhibition	45±2	—23±4	208±12*	43±2,3*	23±1*	31±3*	7±0,3*	1,45±0,4*	23,7±1*	31±0,2*
period of stabilization of shock	62±4*	—20±3	234±10	42±3,8	23±2	27±2	12±1,5*	2,5±0,3*	27±1*	40±3,0*
15 min before end of experiment	26±3*	—28±4	180±19	41±3,7	22±2	48±10*	2±0,3*	0,36±0,1*	32±5*	53±6,0
II. Intravenous injections of procaine in early period of hemorrhagic shock: Initial values	117±3	±32±2	56±2	74±2,4	40±1,2	18±1	21±3,5	1,47±0,3	25	50
phase of inhibition	41±1*	—24±3*	192±9*	38±1,9*	22±2*	31±4*	8±1,1*	1,54±0,4*	20±2*	40±5*
before injection of procaine	56±3*	—28±3	205±8	—	—	31±2	8±2,0	1,53±0,3	23±2	40±5
20-30 min after injection of procaine	90±4*	—36±5	197±10	38±2,2	22±1	18±5*	10±2	1,97±0,3*	33±4	58±9
at end of experiment	96±5	+22±4 —21±8*	184±10	46±2,8	27±2	20±6	11±2,5	2,06±0,6*	33±8	58±8

*Values of indices differing significantly from those at the previous stage of the experiments.

Note. Changes in indices in series III and IV do not differ significantly from changes in series II and they are therefore not given.

TABLE 2. Effect of Intravenous Procaine Injections on Outcome of Posthemorrhagic Reaction

Series of experiments	Number of animals	Volume of blood loss (in ml/kg; M ± m)	Outcome			
			number of survivors	P	duration of survival of animals until death (in min; M ± m)	P
I. Control:						
dogs	13	37,2±1,0	—	—	139±23	—
rabbits	10	23,8±0,3	—	—	35±16	
II. Intravenous injections of procaine in early period of hemorrhagic shock:						
dogs	14	36,6±1,0	12	<0,05	185 и 720	—
rabbits	15	22,8±1,0	13	<0,05	110 и 480	—
III. Intravenous injections of procaine in period of stabilization of hemorrhagic shock:						
dogs	11	38,2±1,1	9	<0,05	305 и 1020	—
rabbits	15	22,7±1,0	13	<0,05	67 и 105	—
IV. Intravenous injections of procaine in late period of hemorrhagic shock:						
dogs	10	38,1±5,0	4	<0,05	216±55	>0,05
rabbits	10	23,0±0,4	3	<0,05	246±37	<0,05
Total:						
dogs	48		25			
rabbits	50		29			

Note. Level of significance shown relative to control series of experiments.

by the lobeline method (injected into the femoral vein), and the stroke and minute volumes of the heart by integral rheography [21]. The results were converted into more adequate systolic and cardiac indices [8]. The principal criteria of effectiveness of intravenous procaine injections were the survival rates and life spans of the animals.

EXPERIMENTAL RESULTS AND DISCUSSION

The dynamics of the posthemorrhagic reaction was studied in series I. Immediately after blood loss a phase of inhibition was observed (marked arterial hypotension, no response to stimulation, predominance of the slow rhythm of the EEG, constriction of arteries of the optic fundus and conjunctiva), and it lasted for 3-5 min. It was followed by the development of the typical symptom complex of hemorrhagic shock, with three distinct periods: early, stabilization, and late. In the early period a gradual rise of the arterial and central venous pressure was observed, together with briskness of responses to stimulation, the appearance of fast components on the EEG, and improvement of the other indices studied; in the period of stabilization these underwent little change. The late period was characterized by a steady fall of arterial pressure, the appearance of regular slow waves on the EEG with disappearance of rhythm-binding responses, a gradual worsening of the ECG and EMG indices, and a progressive disturbance of the microcirculation (as shown by measurements of the vessels of the optic fundus and conjunctiva). The terminal state soon supervened and all the animals died (Table 1).

The results of these experiments confirmed earlier observations [23] showing that the periods of hemorrhagic shock reflect quite distinct functional states of the body. In each subsequent series, therefore, procaine in a 1% solution was injected in doses of 10 mg/kg (into the femoral veins of the dogs and into the marginal veins of the ears of the rabbits) at the different periods of shock, occurring at different times after blood loss. Since the functional state of the animals initially before injection of procaine was the same in each series, reliable data for the effect of the procaine could be obtained.

Injection of procaine in the early period of hemorrhagic shock led to an increase in the stroke and minute volumes of the heart, a decrease in the lobeline time (an increase in the velocity of blood flow), constriction of the veins, and disappearance of spasm of the arterioles of the microcirculation. Against this background the arterial pressure gradually rose and the other indices improved, although they had not regained their initial values by the end of the experiment. Most of these animals survived (Table 2).

Intravenous injections of procaine in the period of stabilization show the same results. Injection of procaine in the late period of hemorrhagic shock was less effective, although the survival rate was significantly higher and the life span of the animals was lengthened.

Intravenous injections of procaine thus prevent development of the late period of hemorrhagic shock and, in particular, its irreversible stage; i.e., they have a significant effect on the outcome of the posthemorrhagic reaction. Presumably the positive effect of procaine is due to its ability to modify reflexes [18] and to increase the output of the heart as a result of constriction of the capacitive vessels and increased sensitivity of resistive vessels to adrenalin [1, 13], and also of increased tone of the vasomotor center [12]. In addition, the therapeutic effect of procaine in acute blood loss could be connected with the effect of its hydrolysis products on metabolism [10], disturbances of which play an important role in the formation of the late period of shock [16]. The hypobiotic properties of procaine [2, 5, 11, 22], increasing the resistance of the nervous system to anoxia, evidently are of considerable importance. Finally, the broad spectrum of action of procaine indicates that it has a substantial normalizing influence on higher regulatory mechanisms [15], so that it can retard the course of the pathological process induced by acute massive blood loss.

LITERATURE CITED

1. V. A. Babichev, Farmakol. Toksikol., No. 3, 30 (1957).
2. V. A. Babichev, Farmakol. Toksikol., No. 5, 584 (1965).
3. E. N. Budygaev and I. Sh. Blyumin, Vrach. Delo, No. 2, 163 (1956).
4. M. G. Weil' and G. Shubin, The Diagnosis and Treatment of Shock [in Russian], Moscow (1971).
5. E. N. Vorotyntseva, Éksper. Khir., No. 1, 91 (1965).
6. A. C. Guyton, Circulatory Physiology: Cardiac Output and Its Regulation, Saunders, Philadelphia (1963).
7. N. D. Gashimov, Azerbaidzhan. Med. Zh., No. 1, 61 (1966).
8. M. I. Gurevich, in: The Physiology of the Cardiac Output [in Russian], Kiev (1970), pp. 80-87.

9. E. A. Damir, N. M. Sadykov, and V. P. Pastushenko, Khirurgiya, No. 8, 42 (1966).
10. A. S. Konnikova and R. N. Korotkina, Éksper. Khir., No. 6, 61 (1965).
11. M. I. Kuzhman, Éksper. Khir., No. 2, 62 (1969).
12. A. S. Kucheruk, Farmakol. Toksikol., No. 1, 14 (1958).
13. A. S. Kucheruk, Farmakol. Toksikol., No. 5, 555 (1962).
14. Yu. M. Levin, The Regional Circulation in Terminal States [in Russian], Moscow (1973).
15. I. B. Mazhbich, Trudy Omsk. Med. Inst., 45, 171 (1963).
16. I. R. Petrov and G. Sh. Vasadze, Irreversible Changes in Shock and Blood Loss [in Russian], Leningrad (1972).
17. V. I. Popov, P. K. D'yachenko, and A. A. Robin, Éksper. Khir., No. 6, 70 (1965).
18. T. V. Pravdich-Neminskaya, Éksper. Khir., No. 6, 70 (1968).
19. G. M. Solov'ev and G. G. Radzivil, Blood Loss and Regulation of the Circulation in Surgery [in Russian], Moscow (1973).
20. I. Teodorescu-Eczarcu, General Surgical Aggressology [in Russian], Bucharest (1972).
21. M. I. Tishchenko, A. D. Smirnov, L. N. Danilov, et al., Kardiologiya, No. 11, 54 (1973).
22. D. A. Kharkevich and M. I. Tishchenko, Byull. Éksperim. Biol. Med., No. 10, 72 (1957).
23. D. M. Sherman, The Problem of Traumatic Shock [in Russian], Moscow (1972).