SODIUM THIOSULFATE IN THE TREATMENT OF EARLY POSTISCHEMIC DISORDERS

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Substances containing sulfhydryl groups are nowadays being used on an ever-increasing scale as antidotes for intoxications and poisonings. Sodium thiosulfate (ST), for instance, the simplest mineral sulfhydryl compound, plays an active role in the synthesis of organic thiol compounds. ST metabolism is closely linked with metabolism of the low-molecular-weight thiols, one of whose functions is to protect the sulfhydryl groups of enzymes against oxidation and to preserve them in the active form [4, 14, 16]. Research into the use of ST in tourniquet shock, in conjunction with other preparations [1], and in visceral and burn shock in order to improve the renal blood flow [3, 13] have been published in the Soviet literature.

It was accordingly decided that it would be useful to study the effect of ST on the state of the cardiodynamics and central hemodynamics in the early period of postischemic disorders, and the investigation described below was carried out for this purpose.

EXPERIMENTAL METHOD

Experiments were carried out on 64 dogs of both sexes weighing 15-25 kg under intravenous hexobarbital anesthesia. Two experimental models were used: 1) tourniquet shock, induced by application of a hemostatic tourniquet to the base of the hind limb of dogs for 6 h, after which it was removed (35 dogs); experimental myocardial infarction, induced by ligation of the descending branch of the coronary artery at the level of origin of its first branch (29 dogs).

In all experiments the arterial pressure (AP), the pressure in the left ventricle (VP), the stroke volume (SV), the cardiac output (CO), total peripheral resistance (TPR), work of the heart (WH), maximal and minimal rates of development of pressure (dp/dt_{max} and dp/dt_{min}), and excitability and conductance of the myocardium based on the threshold of ventricular fibrillation (VFT), were determined. The values of these indices were recorded on the Siemens-Elema-81 Mingograph, the Nikotron flowmeter, and an instrument for determining VFT designed at the Institute of Clinical and Experimental Medicine, Czechoslovak Ministry of Health. Four series of experiments were carried out to study the state of the cardiodynamics and the central hemodynamics: 1) in the early period of tourniquet shock; 2) after injection of ST in a dose of 500 μg/kg body weight 30 min after removal of the tourniquet; 3) in the early period of experimental myocardial infarction; 4) in the early period of experimental myocardial infarction with administration of ST in a dose of 500 mg/kg body weight 15 min after ligation of the coronary artery. Observations continued for 2 h. The results were subjected to statistical analysis and the significance of differences in the control and experimental values was determined by Student's t-test. Indices for the state of the cardiodynamics and central hemodynamics before removal of the tourniquet and induction of experimental myocardial infarction were taken as 100%.

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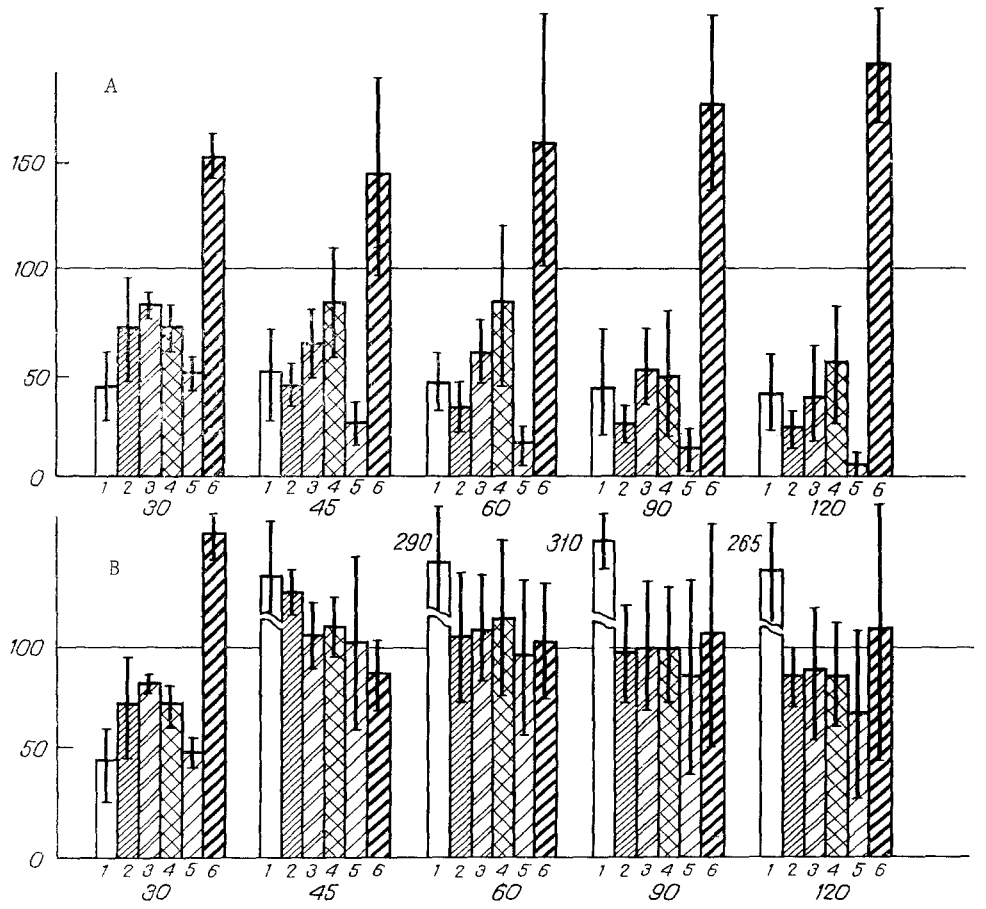

Fig. 1. Indices of cardiodynamics and central hemodynamics in tourniquet shock. Here and in Fig. 2: 1) VFT, 2) CO, 3) AP and VP, 4) dp/dt_{max}, 5) WH, 6) TPR. A) Control, B) administration of ST. Abscissa, value of indices (in % of control); ordinate, time after removal of tourniquet (in min).

EXPERIMENTAL RESULTS

Removal of the tourniquet from animals with tourniquet shock led after the first few minutes to sharp changes in all indices studied: a fall in AP, VP, SV, and CO, a fall in dp/dt_{max} and dp/dt_{min}, a sharp rise in the values of WH and VFT, and a considerable increase in TPR (Fig. 1). Injection of ST against this background caused an increase in AP, VP, SV, CO, dp/dt_{max} and dp/dt_{min}, WH, and VFT, and a decrease in TPR after only 15 min ($P < 0.05$). Later the mean level of AP was close to its initial value, without any marked tendency to fall, whereas VP had an unstable tendency to fall after the 90th minute, although it still remained significantly higher than in the control ($P < 0.05$), and CO remained at its initial level for 90 min, falling subsequently toward the end of the experiment although it still remained 65% higher than the control. The values of dp/dt_{max} and dp/dt_{min} remained at a high level for 1 h after injection of ST. The value of WH was 3 or 4 times higher than in the control throughout the period of observation, but TPR remained at its original level. Injection of ST increased VFT and until the end of the period of observation its value remained higher than in the control.

In experimental myocardial infarction there was no change in AP and VP during the first 15 min after ligation of the coronary artery, but SV and CO, dp/dt_{max} and dp/dt_{min}, and WH all fell, VFT fell sharply, but TPR increased (Fig. 2). After injection of ST, both SV and CO increased, VP remained unchanged, AP rose by 10%, and dp/dt_{max} and dp/dt_{min} increased; WH and TPR fell to the initial level. Later VP remained the same as in the control, but AP, SV, and CO were within the limits of the original value, remaining higher than in the control series ($P < 0.05$). The values of dp/dt_{max} and dp/dt_{min} were higher throughout the period of observation than in the control ($P < 0.05$). WH remained high during the first 30 min after injection of ST, but later this index fell to its original level while still remaining sig-

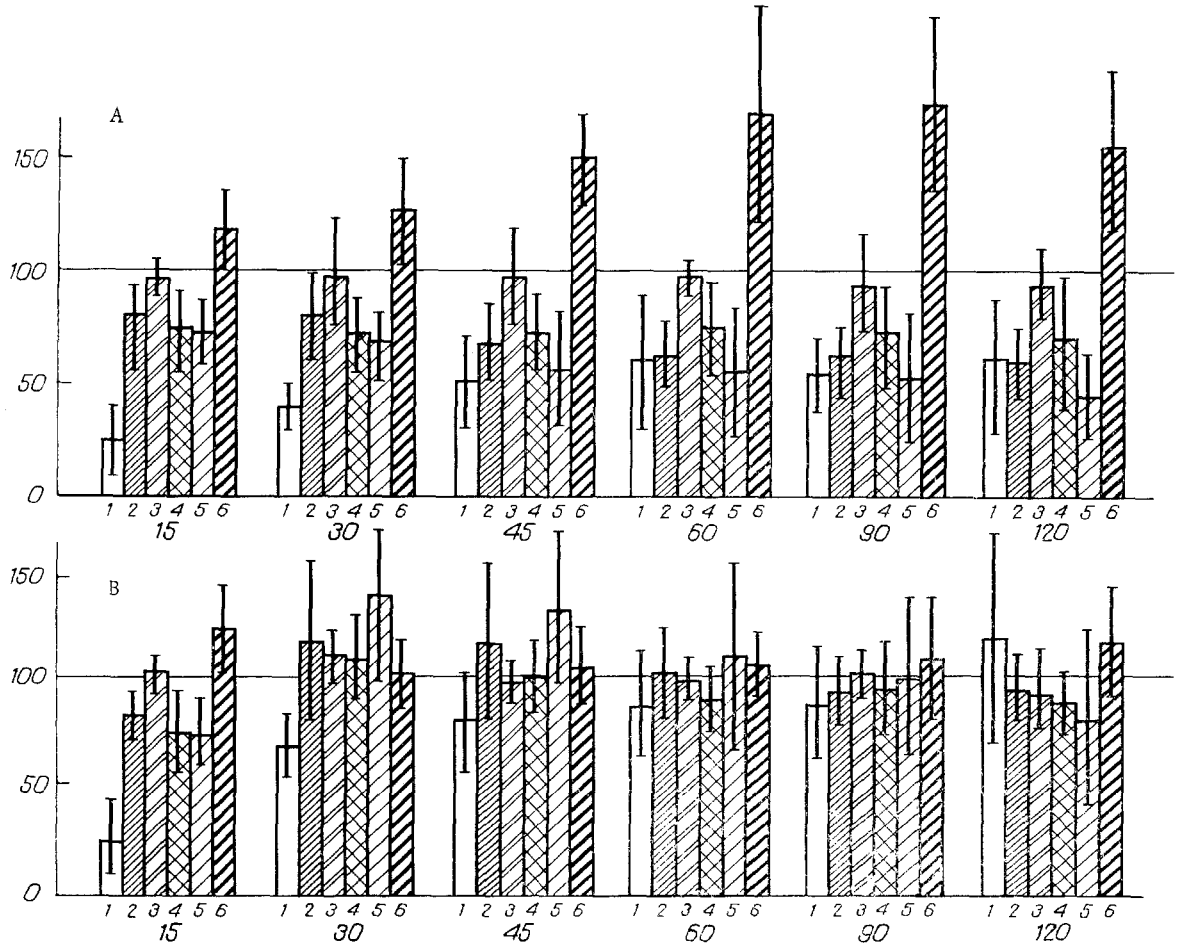

Fig. 2. Indices of cardiodynamics and central hemodynamics in experimental myocardial infarction. Ordinate, time after ligation of artery (in min). Remainder of legend the same as in Fig. 1.

nificantly higher than in the control; TPR was 100-115% of the initial level and was significantly lower than in the control. ST led to a sharp improvement in the value of VFT, bringing it close to its initial level throughout the period of observation.

These investigations revealed a positive action of ST in the early period of development of disturbances of the cardiodynamics and central hemodynamics in postischemic states. An increase in AP and VP must be noted after injection of ST (in tourniquet shock), but no change in these indices in myocardial infarction. The considerable improvement in the state of excitability and conductance of the myocardium will be noted, as reflected in the values of VFT in both experimental models. In all experiments TPR fell under the influence of ST, and the fall was more marked when the disturbances were more severe (tourniquet shock). The action of ST was most effective during the first 15 min after its injection, when a considerable increase in contractility of the heart and temporary lowering of peripheral vascular tone were observed. The positive effect of ST lasted 1.5-2 h.

The mechanism of action of ST may be linked with correction of sulfur metabolism. For instance there are indications that in ischemia, hypoxia, burns, andother types of trauma the blood and tissue levels of sulfhydryl groups show a distinct fall [6, 12, 14, 15, 16]. Sulfur-containing preparations in many cases produce a therapeutic effect in subtoxic or toxic doses [4]. In the early postischemic period a considerable increase is observed in the blood level of a biologically active substance, namely ischemic toxin [10]. According to existing data, ischemic toxin isolated from the perfusion fluids of various organs (limb, heart, small intestine) [11] can interact with sulfhydryl groups [7]. Meanwhile, injection of thiol groups into donors prevents the action of ischemic toxin on mitochondrial membranes [2, 7, 8]. Injection of ST increases the concentration of sulfhydryl groups in the body [4, 5, 9]. The action of ST in acute circulatory disturbances is evidently connected with stimulation of

intracellular metabolism, with elevation of the blood and tissue levels of sulfhydryl groups, and with its action as an antidote against ischemic toxin.

Injection of ST thus gave a marked positive effect in acute circulatory disturbance associated with tourniquet shock and experimental myocardial infarction; it improved contractility, activity, excitability, and conductance of the myocardium and helped to restore the normal peripheral circulation.

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