TOXIC ACTIVITY OF BLOOD PLASMA IN THE EARLY POSTRESUSCITATION PERIOD

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Critical states developing as a result of trauma, blood loss, shock, and acute renal failure are accompanied by marked endogenous intoxication, the principal toxic agents of which are tosic peptides of average molecular weight [4, 5, 8, 10]. These toxic substances possess cardiodepressive activity [9] and, in some cases, neurotropic activity also [6, 7]. Endogenous intoxication is also one of the main pathogenetic factors of postresuscitation sickness [2]. Its nature has not yet been finally settled.

The aim of this investigation was to determine the nature of the toxic activity of blood plasma of animals recovering from clinical death in the early stages of the postresuscitation period.

EXPERIMENTAL METHOD

Experiments were carried out on ten dogs under superficial pentobarbital anesthesia (3 mg/kg) after premedication with trimeperidine (8 mg/kg). Clinical death developed as a result of acute blood loss from the femoral artery. The duration of suffering was 8.03 ± 1.25 min and of clinical death 10 min. Intra-arterial infusion of blood with adrenalin, intravenous blood infusion, artificial ventilation of the lungs and, if necessary, indirect cardiac massage and electrical defibrillation were used for resuscitation. In the initial state and again 10, 30, and 60 min after the beginning of the resuscitation measured samples of arterial blood were taken for determination of the acid–base balance, toxicity of the blood plasma (by bioassay in mice with blocked reticuloendothelial system) [1], and the gel-chromatographic spectrum of the plasma. Gel filtration was carried out on columns measuring 50 × 1.5 cm. Sephadex G-75 was used as the carrier. Elution was carried out with 0.9% NaCl solution at the rate of 0.6 ml/min. The zone of application corresponded to 0.4 ml. The collected fractions (34 from each sample of plasma) were detected in UV light at a wavelength of 254 nm. Ovalbumin (molecular weight (MW) 40,000 daltons), cytochrome c (MW. 12,300 daltons), vitamin B_{12} (MW 1350 daltons), and creatinine (MW. 113 daltons) were used as markers.

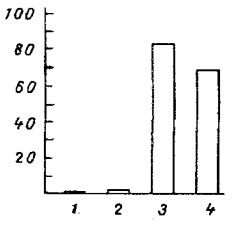

Fig. 1. Dynamics of toxicity of blood plasma in postresuscitation period. Abscissa, 1) initial data; 2) after 10 min; 3) 30 min; 4) 60 min of postresuscitation period; ordinate, death of mice after injection of plasma (in percent).

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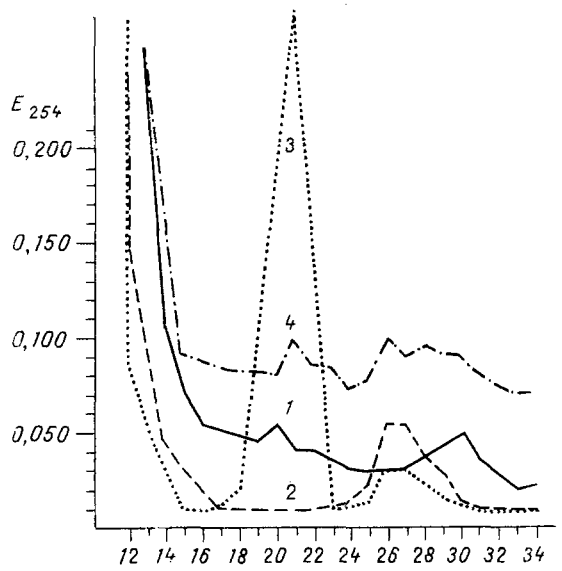

Fig. 2. Gel-chromatographic spectrum of blood plasma of dog No. 3 in postresuscitation period: 1) initial data, 2) after 10 min, 3) 30 min, 4) 60 min of resuscitation period. Abscissa, Nos. of fractions.

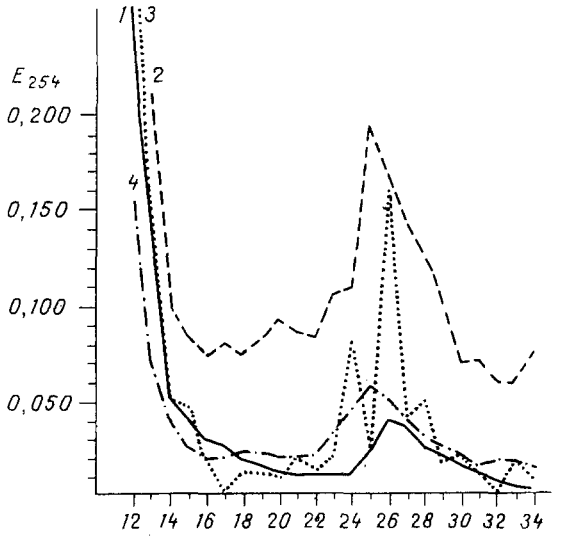

Fig. 3. Gel-chromatographic spectrum of blood plasma of dog No. 7 during postresuscitation period. Legend as in Fig. 2.

EXPERIMENTAL RESULTS

Hypoxia developing as a result of lethal blood loss and, in particular, during the period of circulatory arrest, leads to an abrupt disturbance of metabolism. Products of disturbed metabolism accumulating in the tissue enter the blood stream after the first few minutes of restoration of circulation. Uncompensated metabolic acidosis with a shift of pH to 7.03 ± 0.02 and with an increase in the acid excess to 21.7 ± 1.5 meq/liter was observed in the blood sample taken at the 10th minute of resuscitation. The toxic properties of the plasma were virtually undetectable in this sample. As investigations showed, systemic acidosis acting on several functional systems does not affect the development of toxic properties detectable by bioassay. For instance, on injection of plasma containing 10 mM lactic acid, and with pH 3.0, into mice with a blocked reticuloendothelial system, no toxicity could be found.

The maximal increase in the toxic properties of the blood plasma was observed at the 30th minute of the resuscitation period (Fig. 1). Toward the end of the first hour toxicity remained very high, whereas the acidotic shift in the blood gradually disappeared. Previously on the basis of analysis of data in the literature and the writers' own observations on the effectiveness of adsorbents with porous structure of different kinds in the postresuscitation period the writers postulated that toxic properties of the blood plasma are attributable mainly to toxic fractions of average molecular weight [3].

The results of the present experiments show that in the early postresuscitation period, irrespective of the duration of the period of suffering, a disturbance of homeostasis of components corresponding to fractions of low and average molecular weights is found in the animals' blood. An increase in ultraviolet absorption of the isolated fractions varies from four to six times the initial level. As Fig. 2 shows, in experiment No. 3, in which the duration of suffering was 13 min 15 sec, 10 min after the beginning of resuscitation measures, (sample 2) an increase was observed in absorption of fractions corresponding to components with MW of 100-1500 daltons. Meanwhile a marked metabolic acidosis (BE = 22.7 meq/liter) was observed, but the toxic properties of the plasma were weak. An increase in ultraviolet absorption of high-molecular-weight fractions with a decrease in absorption of fractions of the corresponding low-molecular-weight components occurred 30 min after the beginning of resuscitation (sample 3). The acid excess in the blood by this time showed a small decrease (BE = 18.0 meq/liter). The toxic activity of the plasma was clearly observed: Mortality among the mice was 83%. Disappearance of peaks in all regions studied was observed after 60 min of the resuscitation period (BE fell to 14.3 meq/liter and the toxicity of the plasma to 60%).

A rather different picture was observed in experiment No. 7, in which the period of suffering was much shorter (4 min 20 sec) and the acidotic shift was correspondingly weaker. In sample 2 (peak 3) the peak in the region of low-molecular-weight fractions was ill-defined but absorption was considerably increased in the region of average-molecular-weight components. The acid excess in this sample reached 13.1 meq/liter, but toxic activity was slight (mortality among the mice 30%). In sample 3, with a considerable increase in absorption of fractions with MW of 1000-10,000 daltons, an increase in the toxic properties of the blood plasma was observed to 65%, whereas the acid excess fell to 6.8 meq/liter.

Despite the fact that the duration of suffering and the speed of recovery of the principal vital functions of the body exert some influence on the rate of accumulation of low- and average-molecular-weight components in the bloodstream and their final levels, three phases can be distinguished in the time course of these parameters. The first phase is characterized by flooding of the blood stream with low-molecular-weight components, evidently mainly of the incompletely oxidized products type. The second phase is characterized by a relative fall in the content of low-molecular-weight metabolites and an increase in the content of components with average molecular weight. This phase corresponds to the time of maximal increase in toxic activity of the blood plasma. The rate of development and the duration of this phase depend on the duration and depth of hypoxia in the period of suffering and clinical death and the course of the postresuscitation period. The third phase, which develops by the 60th minute of the postresuscitation period, is characterized by disappearance of peaks in the region of all components studied, together with relative normalization of the acid–base balance of the blood and of functions of the cardiovascular and respiratory systems, recovery of the eye reflexes and of the electrocorticogram, but by marked toxicity of the blood.

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