EFFECT OF DRUGS USED IN COMBINED ELECTROANESTHESIA AND ATARALGESIA ON THE APPEARANCE OF HEPATOSPECIFIC ENZYMES IN THE BLOOD

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Indications for the use of combined electropharmacologic anesthesia (EPA) and its effectiveness in clinical practice are becoming increasingly evident [6, 8]. This is due to recent improvements in the parameters of electrical stimulation (ES), as a result of skin damage beneath the electrodes and tenderness under them in conscious patients [4]. A promising field of application of EPA is during operations on patients with hepatopancreaticoduodenal pathology. However, no attempt has yet been made to compare the effects on the liver of drugs used in combined EPA and ataralgesia (diazepam, droperidol, fentanyl).

As tests of the effects of these drugs and of ES on hepatocytes activity of enzymes of histidine metabolism, namely histidase (histidine-ammonia liase) and urocaninase (urocanate hydratase), in the blood serum was determined. These enzymes are contained only in the liver (except histidase in the skin also) and are not found in other organs and tissues, including blood [1, 2], so that they serve as indicators of side effects of drugs on liver function [3, 5].

The aim of this investigation was to study the effect of the above-mentioned drugs and of ES (components of EPA) on the hepatocyte under experimental conditions.

EXPERIMENTAL METHOD

Experiments were carried out on 204 noninbred male albino rats weighing 200 g, in two groups: 1) healthy animals; 2) a model of acute cholestasis and pancreatitis, produced by ligation of the common bile duct [7]. The following series of tests were undertaken on each group. Series I) ES after preliminary intraperitoneal injection of diazepam (Seduxen) in a dose of 10 mg/kg (premedication). Four nickel foil electrodes measuring 2.5 × 2.5 mm and

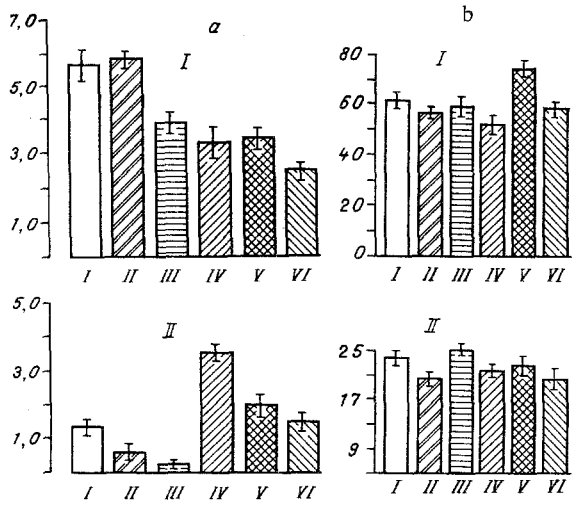

Fig. 1. Histidase (I) and urocaninase (II) activity in healthy animals (a) and in animals with cholestasis and pancreatitis (b) in experiments of series I-VI (M ± m). Ordinate, enzyme activity (in pmoles·ml^{-1}·sec^{-1}). I-VI) Series of experiments. Ten rats were used in each series.

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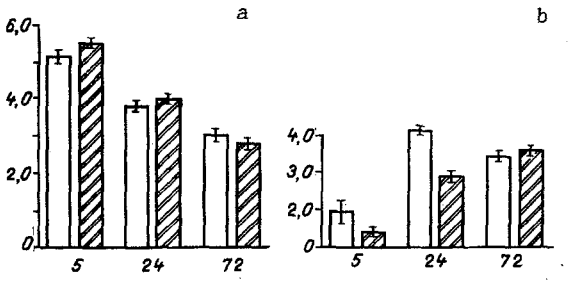

Fig. 2

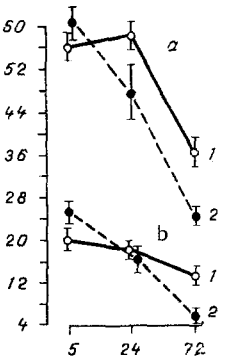

Fig. 3

Fig. 2. Changes in histidase (a) and urocaninase (b) activity in healthy animals 5, 24, and 72 h after two types of procedures. Abscissa, time (in h); ordinate, activity (in pmoles·ml^{-1}·sec^{-1}).

Fig. 3. Changes in histidase (a) and urocaninase (b) activity in animals with cholestasis and pancreatitis 5, 24, and 72 h after two types of procedures. Broken line) ES + diazepam; continuous line) diazepam. Remainder of legend as to Fig. 2.

treated with electrically conducting paste were fixed at four sites on the shaved scalp (the frontal region between the eyes, behind the ears in the parietal regions, and in the occipital region), and through them ES was applied for 5 h. In this series of experiments a further injection of diazepam (5 mg/kg) was given after 2.5 h of ES. The parameters of ES were the same as described previously [4]. The amplitude of the current did not exceed 250 mA. ES evoked neither motor nor autonomic reactions. Series II) Diazepam was injected twice in the above-mentioned doses. Series III) Diazepam (10 mg/kg) and droperidol (2.5 mg/kg) were combined with ES. Repeated doses of diazepam (5 mg/kg) were given 2.5 h, and of droperidol (1.25 mg/kg) 1.5 and 3 h after the beginning of the test. Series IV) Diazepam and droperidol were given at the above-mentioned intervals and doses. Series V) Fentanyl (0.05 mg/kg), with repeated doses (0.025 mg/kg) after 1.5 and 3 h. Series VI) Fentanyl and droperidol at the above-mentioned intervals and doses.

All the animals were fixed in the prone position in a special frame. In series I and II blood was taken from the animals after 5, 24, and 72 h, and in the other series after 5 h. Histidase and urocaninase activity was determined by methods described previously [1, 2].

EXPERIMENTAL RESULTS

In all series of experiments hepatospecific enzymes appeared in the blood of the intact animals 5 h after the beginning of the experiment (Fig. 1). Maximal histidase activity was found in series II (5.70 ± 0.36 pmoles·ml^{-1}·sec^{-1}) and maximal urocaninase activity in series III (0.11 ± 0.025 pmole·ml^{-1}·sec^{-1}). No significant difference was found between the series. Histidase activity after 24 h was reduced in series I and II compared with values recorded after 5 h (Fig. 2), but urocaninase activity was rather higher ($p < 0.05$) in the ES group. After 72 h the levels of the two enzymes were virtually equal in all series (Fig. 2). In animals with cholestasis and pancreatitis the highest histidase activity (Fig. 1) was recorded in series V (fentanyl) 5 h after the beginning of the experiment (73.6 ± 2.3 pmoles·ml^{-1}·sec^{-1}). No difference in histidine activity was found in any other series. No significant differences likewise were observed in urocaninase activity between the series (Fig. 1b). After 24 h histidase activity was significantly lower in series I (by 22%). For urocaninase, after 24 h, a tendency also was observed for activity to fall in series I. After 72 h significant falls were observed in histidase and urocaninase activity (by 30 and 60%, respectively) in series I (Fig. 3).

Analysis of the results reveals differences in the time course of activity of the two organ-specific enzymes. In animals not undergoing bile duct ligation histidase and urocaninase activity corresponded to the minimal hepatotoxic effects of all the types of procedure used. The limits of variation of activity of these enzymes after 24 and 72 h likewise did not exceed permissible values. On the model of acute cholestasis and pancreatitis a considerable

and regular increase in the activity of these enzymes was observed in virtually all the series studied. In this group there was a definite decrease in activity of the hepatospecific enzymes after 72 h in series I with ES by 30 and 60% respectively for histidase and urocaninase (Fig. 3), possible evidence of the hepatoprotective effect of ES.

Drugs used in clinical practice as components of EPA were thus found not to damage the intact liver. On a model of cholestasis and pancreatitis a marked increase in activity of the two enzymes in the blood serum was observed, linked with development of the pathological symptom-complex. In this case administration of fentanyl caused the greatest damage to the liver.

LITERATURE CITED

1. V. A. Burobin, "Determination of histidase and urocaninase in blood: new diagnostic tests for liver damage," Author's abstract of dissertation for the degree of Candidate of Biological Sciences, Moscow (1972).
2. V. A. Burobin and R. N. Korotkina, Some New Methods of Diagnostic Enzymology and Cell Regulation in Clinical Practice [in Russian], Moscow (1982), pp. 21-28.
3. A. A. Karelin, R. N. Korotkina, et al., Vest. Akad. Med. Nauk SSSR, No. 8, 89 (1984).
4. M. I. Kuzin, M. Ya. Avrutskii, et al., Byull. Eksp. Biol. Med., No. 5, 515 (1984).
5. A. A. Panin, R. N. Korotkina, et al., Anest. Reanimatol., No. 5, 24 (1982).
6. G. Burdale-Badie, P. Gardien, et al., Anesth. Analg. Reanim., 37, No. 9/10, 523 (1980).
7. G. Docter-Hünicke and T. Goetze, Acta Biol. Med. Germ., 21, No. 4, 495 (1968).
8. A. Limoge, Rèv. Prat., 33, No. 14, 666 (1983).