PHARMACOKINETICS OF EMOXIPINE IN NORMAL ANIMALS AND MODELS OF EXPERIMENTAL PATHOLOGY

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Emoxipine, a compound of the 3-hydroxypyridine group, is an antioxidant of biogenic type [2]. It is used at the present time in ophthalmologic practice as an angio- and retinoprotector. It has been shown that emoxipine possesses a protective action in myocardial infarction: it limits the size of the infarct, increases the systolic and diastolic fraction of the coronary blood flow, depresses the duration of ventricular fibrillations, and prevents the development of postinfarct heart failure [3, 5].

We have studied the experimental pharmacokinetics of emoxipine after its intravenous injection [6]. A new and promising trend in the development of pharmacokinetic research is the study of the effect of various unfavorable factors on the drug, which is usually carried out under clinical conditions [1]. The aim of this investigation was to study the effect of models of experimental pathology on the kinetics of emoxipine after intravenous infusion.

EXPERIMENTAL METHOD

The pharmacologic experiments were carried out on rabbits weighing 1.8-3.2 kg. Under general anesthesia thoracotomy was performed (after opening of the pericardium the animal was maintained on spontaneous respiration), and an occuluder was introduced beneath the descending branch of the left coronary artery. A catheter was introduced into the femoral vein 24 h later and coronary occlusion carried out for 20 min. Next an aqueous solution of the substance emosipine in a dose of 10 mg/kg was injected into the auricular vein. To study the effect of operative stress, a similar operation was performed, but without insertion of the occluder. The plasma emoxipine concentration was determined before injection and 5, 10, 15, 20, 30, 45, 60, 120, and 180 min after infusion by high-performance liquid chromatography. For this purpose 1 ml of plasma, 0.2 ml of 0.1 N KOH, and 5 ml of toluene were shaken for 1 min on a vibrator, and centrifuged for 30 min at 3000 g; a sample of 4.5 ml of the organic layer was withdrawn and re-extracted with 110 µl of 0.1 N H_2SO_4 for 1 min. After centrifugation the aqueous layer was introduced in two samples, each of 50 µl, into the injector of an "Ultrachrom G-Ti" chromatographic system. Fractionation was carried out on a "Lichrosorb RP-8" column (4.6 × 250 mm) with C_8 precolumn (4.6 × 30 mm), using acetonitrile–diethylamine hydrochloride 0.011 M (55:45 v/v), pH 3.2 (H_3Po_4), as the eluting agent. The samples were analyzed on an LKB-2151 UV-detector at 296 nm, the signal was recorded on an LKB-2210 automatic writer, and the data were analyzed quantitatively by means of a "Hewlett-Packard 3390A" integrator, programmed for calculating areas of peaks. The limit of detection was 25 mg/ml and the retention time 7.3 min. The kinetics of the unchanged preparation was interpreted in accordance with a single-particle model [1].

EXPERIMENTAL RESULTS

Kinetic curves of the blood emoxipine level of the rabbits are given in Fig. 1, and the parameters of kinetics calculated from them in Table 1. A preliminary study of the

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TABLE 1. Pharmacokinetic Parameters of Emoxipine in Rabbits (M ± m)

Parameter	Control	Infarct	Stress
C_0, μg/ml	5,66±0,99	5,26±0,74	4,62±1,07
K_{el}, min^{-1}	0,041±0,008	0,029±0,002	0,030±0,002
V_{app}, liters	5,214±1,026	4,696±0,948	4,842±0,799
Cl^-, ml/min	214,8±42,4	141,9±35,0	171,4±40,4
$T_{\frac{1}{2}}$, min	17,7±2,3	23,7±3.4	21,3±3,0
AUC, μg·ml/min	137,3±30,5	177,1±25,7	153,8±15,0

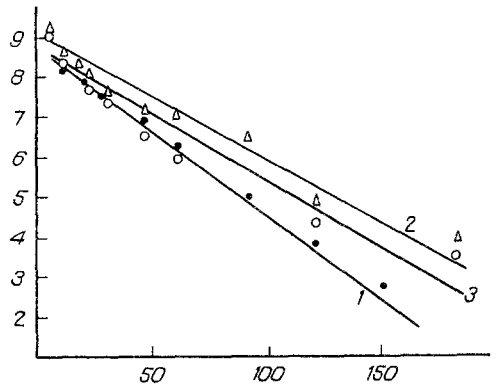

Fig. 1. Profile of plasma emoxipine concentrations in rabbits after a single intravenous injection in a dose of 10 mg/kg. Abscissa, time (in min); ordinate, logarithm of emoxipine concentration (in mg/ml). 1) Control group, 2) animals undergoing infarction, 3) animals with postoperative stress.

pharmacokinetics of emoxipine after intravenous infusion in intact animals demonstrated the following general rules: a high concentration in the initial period, a high rate of elimination, rapid "clearance" of the preparation from the blood, connected with marked penetration into organs and tissues, where the drug is stored and metabolized [6]. No metabolites are found in the blood, which is in agreement with data on the biotransformation of emoxipine [4].

The postinfarct state considerably modifies the pharmacokinetics of emoxipine and changes were especially marked at the stage of distribution and elimination of the drug. Despite closely similar values of initial concentrations of c_0, which evidently indicates a roughly equal strength of pharmacologic action, the profile of Curve 2 in the hypoxic state runs at an appreciably higher level than normally. The rate of elimination of the preparation was reduced, and as a result, its bioavailability increased (as will be clear from a comparison of the areas below the curves). Emoxipine stayed longer in the blood stream (clearance CL 1.5 times less), which is significant, considering that the ischemic organ is the heart, through which the blood flows. Since the apparent distribution volume (V_{app}) did not differ significantly in the two series of experiments, it can be tentatively suggested that the high blood level of emoxipine was due to its reuptake from the depots, which, besides other organs and tissues, may include the ischemic myocardium.

Modification of the kinetics in this way could be explained by exposure of the animal to extremal influences in the form of postoperative stress. However, a stress state was also found to affect the kinetics, but not so severely as the infarct: Curve 3 runs between Curves 1 and 2 (Fig. 1). The rate of elimination (K_{el}) of emoxipine under experimental pathological conditions and during a mock operation was virtually identical, and the half-elimination period ($T_{1/2}$) also was closely similar and within the limits of experimental

error. The plasma emoxipine clearance under stress conditions took place more slowly than normally, but faster than after an infarct. The results are thus evidence of a marked effect of the experimental pathological states on the pharmacokinetics of emoxipine. The possibility cannot be ruled out that similar changes in kinetics will also be observed during its therapeutic use, and this must be taken into account when an adequate system of dosage and optimal schedules of treatment of postinfarct states are worked out.

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INTERACTION OF CARNOSINE WITH SUPEROXIDE RADICALS IN AQUEOUS SOLUTIONS

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The study of the biological role of the natural skeletal muscle dipeptide carnosine (β-alanyl-L-histidine) has led to the discovery of its marked antioxidative activity [3, 7]. Carnosine was found not only to inhibit ascorbate-dependent membrane lipid peroxidation (LPO) and to interact with lipid conversion products [1], but also to quench singlet oxygen [10] and, in the form of a complex with Zn^{2+} and Cu^{2+}, to exhibit superoxide dismutase activity [2]. Investigation of the antiradical activity of carnosine by pulsed radiolysis may help to shed light on the mechanism of its biological action. There is information in the literature on interaction of carnosine with the primary products of radiolysis of water, but these results were obtained under anaerobic conditions [11, 14]. In the present investigation, eth method of pulsed radiolysis of water under conditions of synchronous spectrophotometric recording of optical absorption of short-living particles was used to study the kinetics of formation and destruction of intermediate radiolysis products in the presence of carnosine under aerobic conditions.

It was concluded from the results that carnosine interacts with the superoxide anion and the OH-radical and that it can form a complex with the superoxide anion with charge transfer with a maximum of absorption at 265 nm.

EXPERIMENTAL METHOD

Pulsed radiolysis of aqueous solutions of carnosine was carried out on the apparatus of the A. N. Frumkin Institute of Electrochemistry, Academy of Sciences of the USSR, using the U12 accelerator (E = 4.5 MeV, τ = 2.2 μsec, dose per pulse 30-40 Gy) and with spectrophotometric recording of the intermediate products thus formed, by the method described pre-

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