biochemical parameters which are changed during the stages of stress may prove to be the most promising stress protectors. These compounds, in particular, include derivatives of nicotinic acid, lithium nicotinate, picamilon (sodium N-nicotinoyl-aminobutyrate), and other preparations capable of raising the PN level during biotransformation in the stressed organism [5]. It can be concluded from these results that one way of making pharmacological correction of the stress syndrome more effective is by the differential use of different groups of stress protectors, depending on the stage of chronic stress.

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PHARMACOKINETICS OF KEMANTANE IN RATS

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The pharmacokinetics of the new Soviet immunostimulator kemantane was studied by gas–liquid chromatography in experiments on noninbred rats. It was shown that after internal administration kemantane is quickly metabolized, with the formation of an active metabolite. Both kemantane and its metabolite are distributed rapidly from the blood into the internal organs. The preparation is excreted mainly in the form of the metabolite from rats.

Kemantane (1-hydroxyadamantan-4-one) is an original nitrogen-free oxygen-containing derivative of adamantane, with no substituent groups in position 2 of the adamantyl radical, which was synthesized in the Institute of Pharmacology, Academy of Medical Sciences of the USSR. The theoretical basis for its development was data in the literature indicating that adamantane-containing compounds possess a range of pharmacological, including anticataleptic, activity for which reason kemantane was initially suggested as a remedy for the treatment of patients with parkinsonism. Clinical trials of kemantane, on too small a scale, have failed to reveal any advantages over midantan [5], currently used in medical practice. Subsequent experimental studies have shown that kemantane possesses immunomodulating properties in animals with depressed immunity, and it also has an inducing effect on the cytochrome P-450 system [3], which provided a basis for its clinical study as a nonspecific immunomodulator. Clinical trials of kemantane have now been successfully concluded and the preparation has been recommended by the Pharmacopoeial Committee of the Ministry of Health of the USSR for

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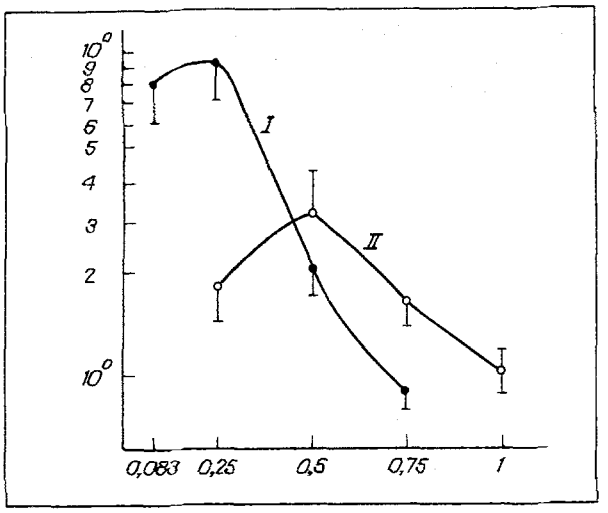

Fig. 1. Kinetic curve of kemantane and adamantane-1,4-diol after oral administration of kemantane in a dose of 50 mg/kg. Abscissa, time (in h); ordinate, concentration of preparation and its metabolite (in μg/ml plasma). I) mantane; II) adamantane-1,4-diol.

TABLE 1. Principal Pharmacokinetic Parameters of Kemantane and Adamantane-1,4-diol

Parameter	Kemantane	Metabolite
K_e, h^{-1}	4,7342	2,1910
$T_{1/2}$, h	0,1464	0,3163
AVC, μg·h/ml	0,1104	0,2308
MRT,	0,3141	0,6339
Cl_p, liters/kg	142,248	216,638
V_d, liters	30,048	93,864

medical use as an immunomodulator [1]. During the stage of the experimental study of kemantane its pharmacokinetics and urinary excretion were studied in rats, and the results are described below.

EXPERIMENTAL METHOD

Experiments were carried out on noninbred male albino rats weighing 180-220 g. Kemantane was admininstered as an aqueous solution in a dose of 50 mg/kg. The rats were decapitated at discrete intervals after injection of kemantane, and their blood was collected in heparinized tubes. Plasma was obtained by centrifugration for 10 min at 3000 rpm. The compound and its metabolite were extracted from plasma with three volumes of chloroform at neutral pH, and the chloroform extracts were evaported to dryness in a rotary evaporator. The dry residues were dissolved in a small volume of ethyl acetate and subjected to gas–liquid chromatography with a flame ionization detector, using a 2-m column filled with 3% OV-17 on Chromaton N. The conditions of chromatography were: T_{column} 175°C, $T_{evaporator}$ 250°C, consumption of carrier gas (highly pure nitrogen) 20 ml/min on leaving the column. The retention time during chromatography under these conditions was: 7 min for kemantane and 8 min 45 sec for the metabolite. Quantitative determination of kemantane and its metabolite were carried out by the absolute calibration method.

Excretion of kemantane was studied in rats after internal administration of the compound in a dose of 100 mg/kg, followed by water loading in a volume of 5 ml daily for 5 days.

EXPERIMENTAL RESULTS

The results of the study of the pharmacokinetics of kemantane are shown in Fig. 1. On oral administration the preparation is quickly and well absorbed: it is found in the systemic circulation 5 min after admininstration, the concentration rises until a maximum after 15 min, after which it falls rapidly between 45 and 60 min after administration, and later the preparation cannot be detected in the rat's blood. Rapid elimination of kemantane into the internal organs was accompanied by the appearance of its principal metabolite in the blood. On the basis of data in the literature and investigations conducted at the Research Institute of Pharmacology on metabolism of other adamantane-containing compounds [2, 4], it was shown that the main direction of their metabolism is the formation of hydroxylated derivatives with the participation of the liver mono-oxygenase system. The results of identification of the structure of the metabolite showed that with the particular preparation used, its metabolite is a hydroxylated derivative; further research into chromatographic behavior of alcohols con-

taining hydroxyl groups in different positions of the adamantane ring, synthesized by the method of retro-organic synthesis, showed that the metabolite was adamantane-1,4-diol. The metabolite had immunostimulating activity similar to that of kemantane.

It will be clear from Fig. 1 that adamantane-1,4-diol appeared in the rats' blood as early as 15 min after internal administration, to reach a peak concentration 30 min after administration, and it was distributed just as quickly (within 1 h) as kemantane from the blood into the internal organs.

On the basis of the results relating to the kinetics of kemantane and its metabolite, the basic pharmacokinetic parameters were calculated by the statistical moments method [6], and these are given in Table 1.

It will be clear from the data in Table 1 that kemantane has a high elimination constant, as a result of which its half-elimination time is very short. Values of AVC and MRT were low. The parameters of the metabolite were similar to those of kemantane. The metabolite also had low values of MRT and $T_{1/2}$, although they were higher than those of kemantane. The metabolite is eliminated from the blood more slowly than kemantane. K_e for the metabolite is less than half that of K_e for the unchanged preparation, possibly due to the prolonged process of formation of the metabolite. Values of the clearance and distribution volumes were greater for the metabolite, possibly due to its greater lipophilicity.

The rapid metabolism of kemantane is probably due to the fact that it contains substituents in its structure in position 2 of the adamantane ring, unlike the 2-substituted derivatives of adamantane, which continue to be present unchanged in the blood for a longer time [2, 4].

The study of the urinary excretion of kemantane by the rats showed that the preparation is excreted over a period of 5 days in the form of its principal active metabolite, excretion of which amounts to only 0.1% of the administered dose of the compound.

Thus these investigations showed that kemantane is quickly metabolized after peroral administration of the compound to rats as a result of the intensive "first passage" effect through the liver. The main metabolite of kemantane is adamantane-1,4-diol, which possesses immunostimulating activity similar to that of kemantane. Kemantane is excreted by rats mainly in the form of adamantane-1,4-diol, excretion of which amounts to 0.1% of the administered dose of kermantane.

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