KINETICS OF ACCUMULATION AND ELIMINATION OF [^{3}H]RIMANTADINE IN TISSUES OF PREGNANT MICE AND FETUSES

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Amino derivatives of adamantane and, in particular, rimantadine (α-methyl-1-adamantanemethylamine), are used in the prevention and treatment of influenza [2, 4, 7]. One of the important pharmacokinetic characteristics of chemotherapeutic preparations for use on large groups of the population, and this of course includes rimantadine, is their ability to pass through the placenta and the dynamics of their accumulation and, in particular, their elimination from fetuses. No appropriate data for rimantadine could be found in the literature.

The aim of this investigation was accordingly to study the kinetics of accumulation and elimination of [^{3}H]rimantadine in fetuses and tissues of pregnant mice.

EXPERIMENTAL METHOD

[^{3}H]rimantadine obtained by the method described previously [5] was used. The specific radioactivity of the preparation was 30 mCi/mmole. Experiments were carried out on noninbred female albino mice weighing 30 g at the 15th-16th days of pregnancy, and also on noninbred albino mice weighing 10-12 g. [^{3}H]Rimantadine was administered perorally in 0.3 ml physiological saline (2.8 mg/kg). At specified times (15 and 30 min, 1, 2, 6, and 12 h after administration of the preparation) the mice were decapitated and the organs removed were transferred into 5 N NaOH (7 ml for fetuses, 5 ml for the liver, and 3 ml each for the kidneys and spleen). The tissues were homogenized and the homogenate was treated with an equal volume of benzene to extract the labeled rimantadine. After vigorous shaking for 10 min the suspension was centrifuged for 15 min at 4000 rpm to separate the benzene from the aqueous phase. Aliquots (0.2 ml for liver and 1 ml each for fetuses, spleen, and kidneys) were taken from each sample and radioactivity determined in 10 ml of toluene scintillator on an SL-30 liquid scintillation spectrometer (Intertechnqiue, France).

TABLE 1. Uptake of [^{3}H]Rimantadine into Fetuses and Organs of Pregnant Mice

Time of investigation	Fetus		Liver		Kidneys		Spleen	
	ng per all fetuses	%	ng per organ	%	ng per organ	%	ng per organ	%
15 min	777	0,8	8538	8,5	254	0,3	58	—
30 min	1186	1,2	7538	7,5	379	0,4	95	—
1 h	1053	1,1	3580	3,6	298	0,3	238	0,2
2 h	726	0,7	1907	1,9	170	0,2	116	0,1
6 h	352	0,4	707	0,7	180	0,2	51	—
12 h	212	0,2	743	0,7	61	—	90	—

Legend. Mean results of six parallel experiments shown. Coefficient of variation of method 14.75% at $P < 0.05$ level. %) Percentage of quantity of rimantadine administered to one animal. —) Under 0.1%.

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TABLE 2. Distribution of [^{3}H]Rimantadine in Tissues of Pregnant (I) and Virgin (II) Mice (ng/mg tissue)

Time of investigation	Fetus	Liver		Kidneys		Spleen	
		I	II	I	II	I	II
15 min	0,1	2,8	2,9	0,3	1,6	0,4	1,2
30 min	0,1	2,5	4,0	0,5	4,7	0,6	2,3
1 h	0,1	1,2	3,5	0,4	3,4	1,4	2,7

Legend. Mean results of six parallel experiments shown. Coefficient of variation of method was 14.5% at P = 0.05 level.

EXPERIMENTAL RESULTS

The results given in Table 1 reflect the distribution of [^{3}H]rimantadine in the fetuses, liver, kidneys, and spleen of pregnant mice during 12 h after administration of the preparation. Its accumulation in the organs studied reached a peak early. After 15 min the maximal content of [^{3}H]rimantadine entering the organ was found in the liver (8.5% of the administered dose per individual mouse). After 30 min 1.2% of administered rimantadine had accumulated in the fetuses and 0.4% in the kidneys. Maximal accumulation of the substance in the spleen occurred 1 h after administration (0.2%).

The results enable the character of elimination of rimantadine from fetuses, liver, kidneys, and spleen of pregnant mice to be studied. The half-elimination time of the substance from the fetuses and all the organs studied did not exceed 2 h (Table 1). Traces of rimantadine (under 0.1%) were found 12 h after administration in the kidneys and spleen, 0.2% remained in the fetuses, and about 0.7% of the preparation in the liver.

These results are in good agreement with those of the writers' previous investigation of the distribution of rimantadine in the tissues of virgin mice [3] and also with the results obtained by workers in other countries who have studied the pharmacodynamics of rimantadine (1-adamantanamine), another derivative of the adamantane series [6, 8].

The dynamics of accumulation and elimination of rimantadine in pregnant mice thus does not differ from that in virgin animals.

Table 2 gives the results of a comparative study of the distribution of [^{3}H]rimantadine in the tissues of pregnant and virgin mice during the period of maximal accumulation of the drug (30 min and 1 h after administration). In virgin animals the tissues of the kidneys and liver have the greatest capacity for accumulation of rimantadine (4.7 and 4.0 ng/mg, respectively), as shown by the concentration of [^{3}H]rimantadine per milligram tissue, and splenic tissue has a much smaller capacity (2.7 ng/mg). The highest concentration of rimantadine in pregnant mice was found in the liver (2.5 ng/mg), followed by the spleen (1.4 ng/mg) and kidneys (0.5 ng/mg). The lowest concentration of rimantadine (0.1 ng/mg) was found in the fetuses.

The character of accumulation of the substance in pregnant mice thus shows certain differences compared with virgin mice: The very low uptake of [^{3}H]rimantadine into the kidneys of pregnant animals will be noted.

It can be concluded from the results of this investigation that the placenta is readily permeable to rimantadine and that it is completely eliminated from the fetus in this particular model. Absence of a carcinogenic and teratogenic action of rimantadine when injected into mice in a concentration of 300 mg/kg was demonstrated previously [1]. It will be interesting to undertake a similar investigation on large animals and, in particular, on primates.

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