PHARMACOKINETICS OF METHINDIONE, A NEW ANTICONVULSANT

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The pharmacokinetics of the new anticonvulsant, methindione, carbon-labeled in the carbonyl and N-methyl groups, was studied in experiments on rats. Methindione is quickly absorbed from the gastro-intestinal tract and passes easily through tissue barriers. The highest concentration of methindione in the brain is observed 15-30 min after administration. The metabolism of methindione and its elimination from the tissues take place rapidly. In most tissues only 6-23% of its maximal concentration still remains after administration of the drug. Metabolites of methindione, labeled in the carbonyl group, are excreted mainly through the kidneys, but metabolites labeled in the N-methyl group are excreted chiefly through the lungs.

KEY WORDS: methindione; pharmacokinetics.

Methindione, a new anticonvulsant prepared in the Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR [1], is the hydrohexachloride of 2-methylamino-2-ethylindandione-1,3. Experiments on animals have shown that methindione has high anticonvulsant activity. Its action, if injected parenterally, appears after 3-5 min, and if given orally after 15 min [2].

The object of this investigation was to study the distribution of methindione in the organs and biological fluids and the pathways and rate of its elimination from the body.

EXPERIMENTAL METHOD

Experiments were carried out on male albino rats weighing 200-280 g. Methindione carbon-labeled in the carbonyl group (3-C^{14}-M; specific radioactivity 80 μCi/g) and in the N-methyl group (N-$C^{14}H_3$-M; specific radioactivity 40 μCi/g) were used. The preparations (14 μCi/g) were given by mouth in aqueous solution. The total dose of the preparation was 350 mg/kg for N-$C^{14}H_3$-M and 175 mg/kg for 3-C^{14}-M. The animals were decapitated 15 and 30 min and 1, 2, 4, 8, and 24 h after administration of the preparations. Blood serum and homogenate of the brain, liver, kidneys, spleen, wall of the small intestine, skeletal muscles, and adipose tissue were taken for investigation. Urine was collected during the experiment in special metabolic cages. The radioactivity of the samples was determined on the USS-1 liquid scintillation counter. The results were expressed in counts/min/g tissue of 1 ml biological fluid. The binding of methindione with the blood serum protein of rabbits was studied by the method of equilibrium dialysis [3]. To compare the empirical curves reflecting the dynamics of accumulation of radioactive substances in the urine, the method of regression analysis [4] was used.

EXPERIMENTAL RESULTS

The results (Fig. 1) demonstrated the considerable differences in the dynamics of the radioactivity of the blood serum after administration of 3-C^{14}-M and N-$C^{14}H_3$-M. The differences can be explained by the fact that during metabolism of the labeled methindione preparations the label remained in different

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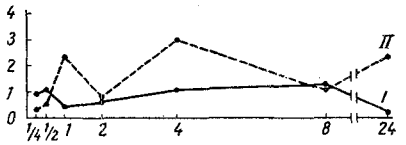

Fig. 1

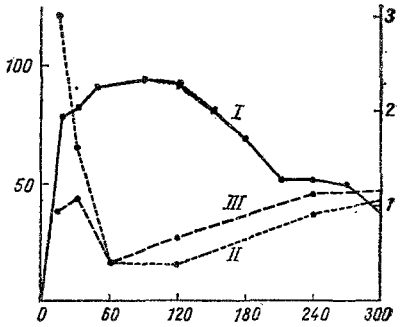

Fig. 2

Fig. 1. Level of radioactivity in blood serum of rats after oral administration of 3-C^{14}-M (I) and N-$C^{14}H_3$-M (II). Abscissa, time (in h): ordinate, radioactivity (in counts/min/ml · 10^3).

Fig. 2. Dynamics of anticonvulsant effect (I) of methindione and level of radioactivity in the brain (II) and serum (III) of rats after oral administration of 3-C^{14}-M (14 μCi/g). Anticonvulsant dose of methionine 20 mg/kg. Abscissa, time (in min); ordinate: on the left, anticonvulsant activity (in % of maximal), on the right, radioactivity (in counts/min/ml · 10^3).

fragments of the molecule, undergoing a different fate in the body. The dynamics of concentration of the anticonvulsant principle of methindione in the blood serum probably reflected the radioactivity detectable after administration of 3-C^{14}-M predominantly, for this preparation is labeled in the stable part of the molecule. However, this hypothesis is valid only for the first 60 min of the investigation, for later the radioactivity increased with a decrease in the anticonvulsant activity of the preparation*, and it was evidently due not to the methindione itself, but to its metabolites (Fig. 2).

The results of a study of the dynamics of distribution of 3-C^{14}-M and N-$C^{14}H_3$-M in the organs are given in Table 1. The high level of radioactivity detectable in all organs between 15 and 30 min after administration of 3-C^{14}-M is evidence that the compound is rapidly absorbed from the gastro-intestinal tract and passes readily through the tissue barriers, including the blood–brain barrier. After 60 min not more than 6-23% of the maximal concentration of the preparation remained in most of the organs.

When N-$C^{14}H_3$-M was used a high level of radioactivity was observed 1 h after administration. The maximal radioactivity was found in the liver. It can therefore be assumed that in this case the principal

*The anticonvulsant activity was studied in the Laboratory of Pharmacology of the Institute by Candidate of Medical Sciences S. K. Germane, using the maximal electric shock test [5].

TABLE 1. Concentration of Radioactive Products in Organs of Rats After Oral Administration of 3-C^{14}-M and N-$C^{14}H_3$-M (mean of five experiments)

Radioactive preparation	Time after administration (in h)	Radioactivity (in counts/min/g)						
		brain	liver	kidneys	spleen	small intestine	skeletal muscles	adipose tissue
3-C^{14}-M	1/4	2 987	5 987	5 275	831	10 812	1 887	15 617
N-$C^{14}H_3$-M		667	1 300	2 283	0	3 200	1 250	1 267
3-C^{14}-M	1/2	1 650	4 350	4 275	1 316	14 437	2 237	3 930
N-$C^{14}H_3$-M		1 017	2 150	2 983	275	2 283	783	517
3-C^{14}-M	1	437	1 400	325	50	5 109	1 375	1 937
N-$C^{14}H_3$-M		3 217	11 150	5 383	—	—	—	—
3-C^{14}-M	2	412	1 775	1 637	25	2 875	925	6 212
N-$C^{14}H_3$-M		383	383	400	—	—	—	—
3-C^{14}-M	4	925	2 012	112	1 300	7 501	1 937	1 746
N-$C^{14}H_3$-M		133	2 183	233	—	—	—	—
3-C^{14}-M	8	1 387	4 237	5 812	745	4 507	3 012	500
N-$C^{14}H_3$-M		533	1 167	367	147	2 833	883	633
3-C^{14}-M	24	125	137	475	0	805	87	12
N-$C^{14}H_3$-M		83	1 567	850	—	—	—	—

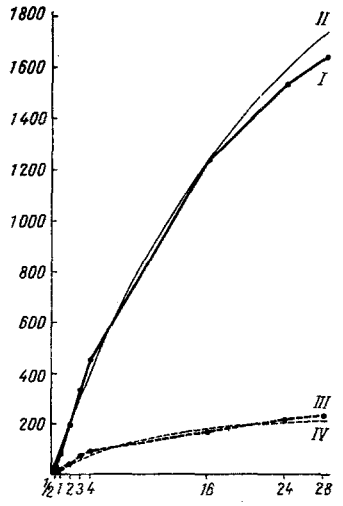

Fig. 3. Accumulation of radioactive products in urine of rats after oral administration of 3-C^{14}-M (I, II) and N-$C^{14}H_3$-M (III and IV). I and III) empirical curves, II and IV) theoretical curves. Abscissa, time (in h); ordinate, radioactivity (in counts/min/total volume of urine · 10^3).

form of methindione metabolism was thus connected with removal of the radioactive CH_3-group. By 2 h the radioactivity due to administration of the N-$C^{14}H_3$-M was sharply reduced.

The supplementary increases in radioactivity in the tissues observed 1-2 h after administration of the labeled preparations, at a time of decreasing anticonvulsant activity of the methionine, were evidently due to breakdown products of the preparation migrating from the tissue depots into the blood serum, and thence into the tissues.

The results of the study of the excretion of methindione from the body are given in Fig. 3. In 28 h only 8.5% of the administered radioactivity of N-$C^{14}H_3$-M and 92.5% of the radioactivity of 3-C^{14}-M were excreted with the urine. Possibly during metabolism of the compound the methyl group is removed and converted by oxidation into formaldehyde, then into carbon dioxide, which is excreted by the lungs. The preparation 3-C^{14}-M is less prone to undergo metabolic conversions, and for that reason the label remained for a long time in sufficiently large fragments of the methindione molecule that were excreted chiefly in the urine.

Methindione is thus readily absorbed from the gastro-intestinal tract and passes easily through the blood–brain barrier. The highest concentration of methindione in the brain is observed 15-30 min after its administration. The compound is metabolized and excreted very quickly, evidently because methindione is not bound with the blood serum protein.

LITERATURE CITED

1. S. K. Germane, Ya. Ya. Ozols, A. K. Aren, et al., Khim.-Farm. Zh., No. 11, 35 (1970).
2. S. K. Germane, in: Proceedings of the Third Congress of Pharmacologists of the USSR [in Russian], Kiev (1971), p. 70.
3. G. Ya. Kivman and É. A. Rudzit, Vopr. Med. Khim., No. 4, 369 (1962).
4. N. A. Plokhinskii, Biometrics [in Russian], Moscow (1970), p. 258.
5. L. A. Woodbury and C. A. Swinyard, Am. J. Physiol., 170, 661 (1952).