Distribution of Bemitil in Organs and Tissues of Rats after Single or Repeated Administration

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After single and repeated peroral administration of bemitil to rats this drug was found in the liver, brain, kidneys, spleen, heart, skeletal muscles, lungs, adipose tissue, and testicles. After single treatment accumulation of bemitil was most pronounced in the liver. After repeated treatment the decrease in bemitil concentration in the liver was probably associated with increased elimination of the drug from liver tissue due to intensification of its biotransformation. We conclude that bemitil can accumulate in the blood, but not in tissues.

Key Words: *bemitil; ethylthiobenzimidazole hydrobromide; pharmacokinetics; distribution*

Pharmacokinetics of benzimidazole derivatives is characterized by intensive distribution of these agents from the blood to organs and tissues [1,2,6].

Here we studied the distribution of bemitil in organs and tissues of rats under various conditions of drug treatment.

MATERIALS AND METHODS

Experiments were performed on male outbred albino rats weighing 200-250 g. The animals fed a complete diet, had free access to water, and were kept under natural light/dark cycle. Bemitil (ethylthiobenzimidazole hydrobromide, 100 mg/kg intragastrically) was administered once or repeatedly (course treatment). The rats were decapitated 1 h after single or last treatment. Drug concentration was measured in the whole blood, plasma, erythrocyte mass, liver, brain, kidneys, spleen, heart, skeletal muscles, lungs, adipose tissue, and testicles. The measurements were performed on a gas chromatograph (model 3700) with an electron capture detector equipped with a ^{63}Ni-b-ionization source and glass column (length 2 m, inner diameter 2.5 mm). Chromatron N-Super with 3% liquid phase SE-30 served as the sorbent.

The results were analyzed using Statistica 6.0 software.

RESULTS

After peroral administration of bemitil in a single dose of 100 mg/kg, this drug was found in the whole blood, plasma, and erythrocyte mass (Table 1). Bemitil was selectively accumulated in erythrocytes. Drug concentration in the erythrocyte mass was 1.77-fold higher than in blood plasma. After repeated treatment the concentration of bemitil in the while blood, plasma, and erythrocytes increased by 1.78, 1.07, and 2.27 times, respectively.

After single and repeated treatment the drug was found in all organs and tissues, but its distribution was heterogeneous.

Bemitil rapidly accumulated in liver tissue. One hour after single peroral administration, the concentration of bemitil in the liver tissue was higher than in the whole blood and plasma (by 3.41 and 4.85 times, respectively, Table 1). Kinetic study

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showed that rat liver exhibits high extraction capacity relative to bemitil, which is typical of benzimidazole derivatives [1]. Imidazoles (*e.g.*, benzimidazoles) are excreted with bile and involved in enterohepatic circulation, which increases their life time in the organism [1].

After course treatment, bemitil concentration in the liver was 1.44 times lower than in experiments with single administration of this drug. The tissue/whole blood (k_p1) and tissue/plasma distribution coefficients (k_p2) decreased by 2.56 and 1.54 times, respectively (Table 1). The liver is the main organ accumulating bemitil after single treatment. The distribution coefficients for other organs and tissues remained practically unchanged or decreased after course treatment with bemitil (Table 1). The decrease in bemitil concentration in the liver after repeated treatment does not result from redistribution between organs and tissues, but is associated with increased elimination of the drug from liver tissue due to intensification of its biotransformation.

Permeability of the blood-brain barrier for imidazoles depends on physicochemical properties of the drugs that are determined by chemical structure of radicals in the benzimidazole ring [1-6].

One hour after single administration, bemitil concentration in the brain practically did not differ from that in the whole blood. Bemitil concentration in the plasma was 1.52-fold lower under these conditions (Table 1). Long-term administration of bemitil was accompanied by a 1.38-fold increase in drug concentration in the brain. It should be emphasized that bemitil concentration in the whole blood increased after long-term treatment, which was primarily related to selective accumulation of the drug in erythrocytes. We observed the decrease in k_p1 by 1.29 times. Plasma bemitil concentration did not differ after repeated and single treatment. After the course of treatment, k_p2 was slightly higher compared to that observed in experiments with single treatment (by 1.3 times, Table 1).

One hour after single peroral treatment, the concentration of bemitil in the kidneys was higher than in the whole blood and plasma (by 2.47 and 3.51 times, respectively, Table 1). Long-term administration of bemitil was accompanied by a slight increase in its concentration in the kidneys (by 1.17 times); k_p1 decreased by 34.01%, but k_p2 increased by 9.7%.

After single treatment, bemitil was found in skeletal muscles. One hour after single administration, the concentration of bemitil in skeletal muscles was higher than in the whole blood and plasma. Long-term administration of bemitil was accompanied by a 1.68-fold increase in its concentration in skeletal muscles; k_p1 decreased by 5.38%, but k_p2 increased by 57.2%.

One hour after single administration, bemitil concentration in the heart was higher than in the whole blood and plasma (k_p1, 1.67; k_p2, 2.37). The course treatment with bemitil was accompanied by acceleration of its elimination from the myocardium; k_p1 and k_p2 decreased by 58.68 and 31.22%, respectively (Table 1).

Bemitil was found in the lung tissue of rats. After single treatment, the concentration of bemitil in the lung tissue was higher than in the whole

TABLE 1. Bemitil Concentration in the Whole Blood, Plasma, Erythrocytes, Organs, and Tissues of Rats Exposed to Single or Repeated Treatment with the Drug in a Dose of 100 mg/kg ($M\pm m$, n=5)

Organs and tissues	Single treatment			Repeated treatment		
	concentration, ng/g (ml)	k_p1	k_p2	concentration, ng/g (ml)	k_p1	k_p2
Whole blood	2684.0±380.0	—	—	4766.6±392.0	—	—
Plasma	1888.0±150.0	—	—	2013.4±280.0	—	—
Erythrocytes	3335.0±380.0	—	1.77	7579.7±840.0	—	3.76
Liver	9160.0±760.0	3.41	4.85	6340.0±480.0	1.33	3.15
Brain	2878.0±210.0	1.07	1.52	3980.0±720.0	0.83	1.98
Kidneys	6630.0±520.0	2.47	3.51	7760.0±540.0	1.63	3.85
Spleen	5976.0±870.0	2.23	3.16	4790.0±360.0	1.0	2.38
Heart	4473.0±450.0	1.67	2.37	3290.0±250.0	0.69	1.63
Skeletal muscles	4980.0±480.0	1.86	2.64	8358.0±640.0	1.75	4.15
Lungs	3700.0±410.0	1.38	1.96	3620.0±280.0	0.76	1.8
Adipose tissues	2020.0±620.0	0.75	1.07	2130.0±430.0	0.45	1.06
Testicles	3038.0±580.0	1.13	1.61	2686.0±310.0	0.56	1.33

blood and plasma (by 1.38 and 1.96 times, respectively). Long-term administration of bemitil was accompanied by a decrease in its concentration in the lung tissue; k_p1 and k_p2 decreased by 44.93 and 8.16%, respectively (Table 1)

After single administration the concentration of bemitil in adipose tissue was lower than in the whole blood, but did not differ from that in the plasma. The course of treatment with bemitil was accompanied by acceleration of its elimination from the adipose tissue; k_p1 and k_p2 decreased by 40 and 0.94%, respectively (Table 1).

Bemitil was distributed from the blood to spleen tissue. One hour after single administration, the concentration of bemitil in the spleen was higher than in the whole blood and plasma (by 2.23 and 3.16 times, respectively). The course treatment with bemitil was accompanied by acceleration of its elimination from the spleen. k_p1 and k_p2 decreased by 55.16 and 24.68%, respectively.

One hour after single administration, the concentration of bemitil in the testicles was higher than in the whole blood and plasma (by 1.13 and 1.61 times, respectively). The course treatment with bemitil was accompanied by acceleration of its elimination from the testicles. k_p1 and k_p2 decreased by 50.44 and 17.39%, respectively (Table 1).

Our results indicate that bemitil migrates from the blood to organs and tissues in rats. During repeated treatment the increase in bemitil concentration in the blood is primarily associated with its accumulation in erythrocytes.

REFERENCES

1. A. A. Spasov, L. A. Smirnova, I. N. Iezhitsa, *et al*., *Vopr. Med. Khim*., **48**, No. 3, 233-258 (2002).
2. F. C. Cheng, Y. E. Ho, L. C. Hung, *et al*., *J. Chromatogr*., **949**, Nos. 1-2, 35-42 (2002).
3. M. Molimard, B. Diquet, and M. S. Benedetti, *Fundam. Clin. Pharmacol*., **18**, No. 4, 399-411 (2004).
4. N. V. Nagaraja, S. K. Singht, J. K. Paliwal, and R. C. Gupta, *Pharm. Pharmacol.*, **52**, No. 10, 1253-1263 (2000).
5. S. Sancher, L. Alvarez, J. Sallovitz, and C. Lanusse, *J. Vet. Pharmacol. Ther.*, **23**, No. 4, 193-201 (2000).
6. X. N. Zhang, Q. Zhang, H. Wen, *et al*., *Yao Xue Xue Bao*, **38**, No. 6, 462-463 (2003).