Distribution of Thietazole in Organs and Tissues of Rats after Single and Repeated Administration

S. A. Sergeeva and I. L. Gulyaeva

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We studied the kinetics of thietazole distribution in the liver, brain, kidneys, spleen, heart, skeletal muscles, lungs, adipose tissue, and testicles after single and repeated administration of this drug. Single and repeated administration of thietazole was followed by elimination of this drug from the blood into organs and tissues. After repeated administration, thietazole was selectively accumulated in the spleen.

Key Words: *thietazole; potassium salt of 2-[1-(1,1-dioxythietanyl-3)-benzimidazolyl-2-thio] acetic acid; pharmacokinetics; distribution*

Pharmacokinetic studies are an essential component of preclinical and clinical trials with new medicinal preparations. Studying the rate and intensity of absorption, distribution in organs and tissues, directionality and quantitative characteristics of biotransformation, and pathways and rate of elimination are important for the development, testing, and selection of the optimal pharmacotherapeutic regimen. Thietazole (potassium salt of 2-[1-(1,1-dioxythietanyl-3)-benzimidazolyl-2-thio] acetic acid) has a wide range of biological properties, including the systemic immunoregulatory effect (stimulation of antiinfection resistance, phagocytic activity, and antitumor reactivity; suppression of autoimmunity and transplantation immunity; modulation of the humoral and cellular response; and interferonogenic properties), regulation of enzyme activity of cytochrome P450-dependent monooxygenases, and actoprotector and antioxidant properties [1].

Pharmacokinetics of drugs (benzimidazole derivatives) is characterized by high rate of their distribution from the blood into organs and tissues [2-6].

All-Russian Research Center on Safety of Biologically Active Substances, Staraya Kupavna, Russia. ***Address for correspondence:*** nauka@materiamedica.ru. S. A. Sergeeva

Here we studied the distribution of thietazole in organs and tissues of rats under various routes of 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 the natural light/dark cycle. Thietazole (100 mg/kg intragastrically) was administered one time or repeatedly for 14 days (course treatment). The rats were decapitated 1 h after single administration or after the last treatment. Thietazole 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 by high-performance liquid chromatography using a Beckman gas chromatograph equipped with a Tracor 970A UV detector at 284 nm. Chromatographic separation was performed in a Zorbax-CN column (250×4.6 mm, particle size 5 μ, with 5×4.6-mm precolumn). A mixture of ethanol, water, and glacial acetic acid (45:45:1) served as a mobile phase.

The results were analyzed by Statistica 6.0 software. We calculated the means (M) and errors (m).

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RESULTS

Similarly to other derivatives of benzimidazole (bemitil and ethomerzol), thietazole was selectively accumulated in erythrocytes. Thietazole concentration in erythrocyte mass was 1.97 times higher than in the plasma (Table 1). Thietazole concentration in the whole blood, plasma, and erythrocytes increased by 1.6, 1.73, and 1.54 times, respectively, after course treatment with this drug.

After single and repeated administration, thietazole was found in all organs and tissues. It should be emphasized that the distribution of thietazole was heterogeneous.

Thietazole was accumulated in liver tissue. One hour after single administration, thietazole concentration in the liver was higher than in the whole blood and plasma by 1.19 and 1.82 times, respectively (Table 1). Kinetic study confirmed the fact that rat liver exhibits high extraction capacity to thietazole, which is also typical of other benzimidazole derivatives [4]. Imidazoles, including benzimidazoles, are excreted with the bile and undergo enterohepatic circulation, which increases the life time of these drugs in the organism [4].

After course treatment with thietazole, its concentration in the liver was 1.41-fold higher than after single administration. The tissue/whole blood (k_p1) and tissue/plasma distribution coefficients (k_p2) decreased by 18.7 and 11.8%, respectively (Table 1). The distribution coefficients for other organs and tissues (except for the spleen) decreased after course treatment with thietazole. The decrease in thietazole concentration in the liver after repeated treatment does not result from the redistribution between other organs and tissues, but is associated with increased elimination of this drug from liver tissue due to intensive biotransformation.

Blood-brain barrier permeability for imidazoles depends on physicochemical properties of the drugs that are determined by chemical structure of radicals in the benzimidazole ring.

One hour after single treatment, thietazole concentration in the brain was 79% of its immediate concentration in the whole blood. Under these conditions, thietazole concentration in the brain significantly exceeded that in the plasma (Table 1). Long-term administration of thietazole was accompanied by a 4.46-fold increase in drug concentration in the brain. It should be emphasized that thietazole concentration in the whole blood and plasma increased after course treatment with this drug. Hence, k_p1 and k_p2 remained practically unchanged in the brain.

One hour after single administration, thietazole concentration in the kidneys was lower than in the whole blood and plasma. The distribution coefficients remained practically unchanged after repeated treatment with thietazole. Hence, thietazole concentration in the kidneys was proportional to that in the blood under various routes of treatment (Table 1).

After single administration, thietazole was found in skeletal muscles (k_p1=0.77, k_p2=1.18). Course treatment with thietazole was accompanied by an increase in the rate of elimination from skeletal muscles. k_p1 and k_p2 decreased by 35.1 and 39.8%, respectively.

TABLE 1. Thietazole Concentration in Rats after Single and Repeated Treatment with the Drug in a Dose of 100 mg/kg (*M*±*m*, *n*=5)

Organ, tissue	Single administration			Repeated administration		
	C, ng/g/ml	k_p1	k_p2	C, ng/g/ml	k_p1	k_p2
Whole blood	1067.8±160.0	—	—	1710.85±415.00	—	—
Plasma	699±71	—	—	1210±160	—	—
Erythrocytes	1376±175	—	1.97	2120±381	—	1.75
Liver	1272±320	1.19	1.82	1789±513	1.05	1.48
Brain	843±280	0.79	1.21	1371±314	0.8	1.13
Skeletal muscles	572±150	0.54	0.82	914±132	0.53	0.76
Heart	762±130	0.71	1.09	2228±664	1.3	1.84
Kidneys	745±100	0.7	1.07	796±121	0.46	0.66
Lungs	828±120	0.77	1.18	862±133	0.5	0.71
Adipose tissues	626±130	0.59	0.9	945±162	0.55	0.78
Spleen	517±160	0.48	0.74	575±193	0.34	0.47
Testicles	415±60	0.39	0.59	552±91	0.32	0.46

Note. C, thietazole concentration.

One hour after single administration, thietazole was found in the heart. Course treatment with thietazole was accompanied by acceleration of its elimination from the heart tissue. The distribution coefficients (heart/whole blood and heart/plasma) after repeated administration of thietazole were lower compared to those observed in experiments with single administration of the drug. k_p1 and k_p2 decreased by 34.3 and 38.3%, respectively (Table 1).

One hour after single administration, thietazole concentration in the lung tissue was lower than in the whole blood and plasma (k_p1=0.48, k_p2=0.74). Course treatment with thietazole was accompanied by an increase in the rate of its elimination from lung tissue. k_p1 and k_p2 decreased by 29.2 and 36.5%, respectively (Table 1).

Thietazole was found in the adipose tissue. One hour after single administration, thietazole concentration in the adipose tissue was lower than in the whole blood and plasma (k_p1=0.48; k_p2=0.74). Course treatment with thietazole was characterized by accelerated elimination of the drug from the adipose tissue. k_p1 and k_p2 decreased by 29.2 and 36.5%, respectively.

One hour after single administration, thietazole was found in the spleen (k_p1=0.71; k_p2=1.09). As differentiated from ethomerzol and bemitil, the course of treatment with thietazole was accompanied by selective accumulation of this drug in the spleen. Table 1 shows that the distribution coefficients k_p1 (spleen/whole blood) and k_p2 (spleen/plasma) increase by 83.1 and 68.8%, respectively.

One hour after single administration, thietazole concentration in the testicles was lower than in the whole blood and plasma (k_p1=0.39; k_p2=0.59). Course treatment with thietazole was accompanied by acceleration of its elimination from the testicles. k_p1 and k_p2 decreased by 18 and 22%, respectively (Table 1).

Our results indicate that thietazole administered via various routes is intensively transferred from the blood into organs and tissues. Repeated administration of thietazole is accompanied by selective accumulation of this drug in the spleen [4,6].

REFERENCES

1. R. B. Ibatullina, V. A. Myshkin, S. A. Sergeeva, *et al*., *Med. Truda Prom. Ekol.*, No. 5, 16-19 (2002).
2. S. A. Sergeeva and I. L. Gulyaeva, *Byull. Eksp. Biol. Med*., **141**, No. 5, 534-536 (2006).
3. S. A. Sergeeva and I. L. Gulyaeva, *Ibid*., **145**, No. 1, 47-49 (2008).
4. A. A. Spasov, L. A. Smirnova, I. Ya. Iezhitsa, *et al*., *Vopr. Med. Khim*., **48**, No. 3, 233-258 (2002).
5. F. C. Cheng, Y. E. Ho, L. C. Hung, *et al*., *J. Chromatogr. A*., **949**, Nos. 1-2, 35-42 (2002).
6. X. N. Zhang, Q. Zhang, H. Wen, *et al*., *Yao Xue Xue Bao*, **38**, No. 6, 462-463 (2003).