Comparative Experimental Pharmacokinetics of Benzimidazole Derivatives

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Comparative study of experimental kinetics of distribution of benzimidazole derivatives (bemithyl, etomerzole, and thietazole) in organs and tissues was carried out after single and course treatment. The drugs intensely passed into organs and tissues from the blood after treatment by all protocols. Specific features of drug distribution were detected; for example, splenic tissue selectively accumulated thietazole during course treatment.

Key Words: *bemithyl; etomerzole; thietazole; pharmacokinetics; distribution*

Benzimidazoles are characterized by high intensity of distribution in organs and tissues of experimental animals and humans, cumulation capacity, and pronounced hepatic first-pass effect. The drugs are excreted with the bile and are subjected to enteropathogenic circulation, which prolongs their lifetime in the body. The drugs easily penetrate through the blood-brain barrier [2,3,5-7].

We compared the distribution of three actoprotectors, benzimidazole derivatives bemithyl, etomerzole, and thietazole, in organs and tissues of rats after administration by different protocols.

MATERIALS AND METHODS

The following drugs were used in experiments: bemithyl (2-ethylthiobenzimidazole hydrobromide), etomerzole (5-ethoxy-2-ethylthyobenzimidazole hydrochloride), and thietazole (potassium salt of 2-[1-(1,1-dioxythiethanyl-3)-benzimidazole-2-thio] acetic acid).

Experiments were carried out on outbred albino rats (200-250 g). The animals were kept at natural light on complete rations with free access to water. Bemithyl, etomerzole, and thietazole were administered intragastrically in a single dose of 100 mg/kg or daily in the same dose for 14 days (course treatment). One hour after single or last dose, the rats were decapitated and drug content in the whole blood, plasma, erythrocyte mass, liver, brain, kidneys, spleen, heart, skeletal muscles, lungs, adipose tissue, and gonads was measured. Bemithyl and etomerzole concentrations were measured on a gas chromatograph (model 3700) with electron capture detector containing ^{63}Ni-β-ionization source and a 2-m glass column (inner diameter 2.5 mm). Chromatron N-Super with SE-30 3% liquid phase served as the adsorbent. Thietazole was measured by high performance liquid chromatography on a Beckman chromatograph using Tracor 970-A UV detector at λ= 284 nm. Zorbax-CN column (250×4.6 mm; 5 μ particles; 5×4.6 mm precolumn) was used for chromatographic separation. Eluent consisting of ethanol: water:glacial acetic acid (45:45:1) served as the mobile phase.

The results were processed using Statistica 6.0 software; the means (*M*) and errors in the means (*m*) were calculated.

RESULTS

Bemithyl, etomerzole, and thietazole were detected in all tested organs and tissues after single and course treatment, their distribution being heterogeneous.

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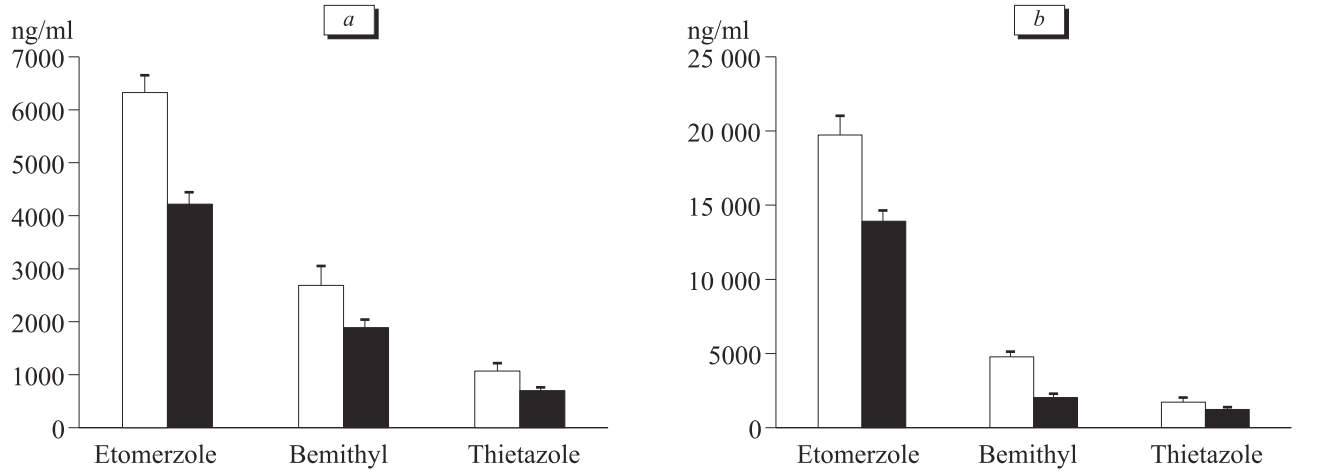

Fig. 1. Content of benzimidazole derivatives in whole blood (light bars) and plasma (dark bars) after a single dose (*a*) and course of treatment (*b*).

The maximum concentrations of bemithyl, etomerzole, and thietazole 1 h after their single oral administration were 2684±380, 6327±328, and 1067.8±160.0 ng/ml in the whole blood and 1890±150, 4218±230, and 699±71.0 ng/ml in the plasma, respectively (Fig. 1). Erythrocytes exhibited selective accumulation of benzimidazole derivatives: drug concentrations in erythrocyte mass after single administration were 1.69-1.97 times higher than in the plasma (Table 1). The concentrations of unchanged preparations in the whole blood were higher after course treatment (Table 1).

Study of the kinetics of benzimidazole derivatives in rat liver confirmed high extraction capacity of tissue towards these drugs (Table 1). Course treatment with etomerzole, bemithyl, and thietazole led to a reduction of the liver/plasma and liver/whole blood distribution coefficients.

The distribution coefficients for the brain, skeletal muscles, heart, kidneys, lungs, adipose tissue, gonads, and spleen virtually did not increase or decreased after course treatment (except thietazole, for which high adsorption capacity of splenic tissue was detected). It seems that lower intensity of benzimidazole derivatives distribution after course treatment is not a result of drugs redistribution in other organs and tissues, but is caused by more intensive elimination of the drugs from the liver tissue because of higher intensity of biotransformation processes.

TABLE 1. Content of Benzimidazole Derivatives in Whole Blood, Plasma, Organs, and Tissues of Rats after Single and Course Treatment (*M*±*m*, *n*=5)

Material	Thietazole (100 mg/kg)				Bemithyl (100 mg/kg)				Etomerzole (100 mg/kg)			
	single dose		course		single dose		course		single dose		course	
	k_d1	k_d2	k_d1	k_d2	k_d1	k_d2	k_d1	k_d2	k_d1	k_d2	k_d1	k_d2
Erythrocytes	—	1.97	—	1.75	—	1.77	—	3.76	—	1.69	—	1.38
Liver	1.19	1.82	1.05	1.48	3.41	4.85	1.33	3.15	11.96	17.93	3.45	4.89
Brain	0.79	1.21	0.8	1.13	1.07	1.52	0.83	1.98	3.42	5.13	4.9	6.94
Kidneys	0.54	0.82	0.53	0.76	2.47	3.51	1.63	3.85	0.72	1.08	0.71	1.0
Spleen	0.71	1.09	1.3	1.84	2.23	3.16	1.0	2.38	0.43	0.65	0.59	0.8
Heart	0.7	1.07	0.46	0.66	1.67	2.37	0.69	1.63	0.55	0.83	0.83	1.18
Skeletal muscles	0.77	1.18	0.5	0.71	1.86	2.64	1.75	4.15	0.63	0.94	0.77	1.09
Lungs	0.59	0.9	0.55	0.78	1.38	1.96	0.76	1.8	1.27	1.9	1.37	1.94
Adipose tissue	0.48	0.74	0.34	0.47	0.75	1.07	0.45	1.06	1.39	2.08	1.01	1.44
Gonads	0.39	0.59	0.32	0.46	1.13	1.61	0.56	1.33	0.15	0.22	0.1	0.14

Note. k_d1: tissue/whole blood distribution coefficient; k_d2: tissue/plasma distribution coefficient.

It is assumed in pharmacokinetics that measurements for the adipose tissue and tissues containing high concentrations of lipids (brain, gonads) are carried out separately from the "muscle group" because of specific distribution of fat-soluble drugs [4]. Estimation of the adipose tissue/plasma (whole blood) coefficient showed that etomerzole was most lipophilic, while thietazole least lipophilic of these derivatives. Course treatment with etomerzole was associated with weak accumulation of the drug in the adipose tissue: the adipose tissue/whole blood distribution coefficient increased by 7.9%, adipose tissue/plasma distribution coefficient increased by 2.1%, while course treatment with bemithyl and thietazole led to their more rapid elimination from the adipose tissue. A similar trend is characteristic of brain tissue: course treatment with etomerzole was associated with minor increase of the brain/whole blood and brain tissue/plasma distribution coefficients (1.43 and 1.35 times, respectively); course treatment with bemithyl was associated with a decrease (1.29 times) in the brain/whole blood distribution coefficient and an increase (by 30.26%) of the brain/plasma distribution coefficient, respectively; course treatment with thietazole led to its accelerated elimination from brain tissue. More rapid elimination of drugs from the adipose tissue could be caused by more intense biotransformation of the drugs as a result of induction of the P-450-dependent monoxygenase system of the liver. In addition, course treatment with all the studied drugs was characterized by their more rapid elimination from gonads.

Physicochemical characteristics of the studied benzimidazole derivatives and hence, their pharmacokinetic parameters (for example, tissue/blood distribution coefficients) indicate that the drugs can exhibit antioxidant activity in hydrophilic and lipophilic phases. The results of our pharmacokinetic studies and the data on LPO processes inhibition by actoprotectors (benzimidazole derivatives) [1] suggest that the protective effect of benzimidazoles can explained by their capacity to modify characteristics of the lipid layers of biomembranes.

Hence, experimental data indicate that bemithyl, etomerzole, and thietazole administered according to different protocols are intensely released into organs and tissues from the blood. The study of drug distribution after course treatment showed that splenic tissue selectively accumulated thietazole.

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