Comparative Analysis of Tissue Availability for Afobazole and Compound M-11

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 149, No. 3, pp. 294-295, March, 2010
Original article submitted November 6, 2009

Comparative analysis of pharmacokinetic parameters of afobazole and its main metabolite M-11 after single intraperitoneal injections of their solutions (25 mg/kg) to rats showed much more intense penetration of M-11 compared to afobazole into rat tissues and organs, judging from the area under the pharmacokinetic curve (AUC) and maximum concentrations (C_{max}). The half-life periods ($T_{1/2e}$l) of afobazole and M-11 were similar.

Key Words: *pharmacokinetics; biotransformation; afobazole; M-11*

An original selective anxiolytic afobazole, 2-(2-morpholinoethylthio)-5-ethoxybenzylimidasole dihydrochloride, was developed at V. V. Zakusov Institute of Pharmacology [2,4,5]. Compound M-11, 2-[2-(3-hydroxymorpholin-4-yl)ethylthio]-5-ethoxybenzimidasole, previously identified as the main afobazole metabolite [3], was synthesized at Department of Chemistry of the Institute by T. Ya. Mozhaeva.

We carried out a comparative analysis of pharmacokinetic parameters of afobazole and compound M-11.

MATERIALS AND METHODS

The study was carried out on outbred male albino rats (200±20 g) from Stolbovaya Breeding Center of the Russian Academy of Medical Sciences. The animals were kept under standard vivarium conditions at 12:12 h day:night regimen. Afobazole and M-11 were injected in aqueous solutions in single doses of 25 mg/kg intraperitoneally. Specimens of the blood and organs were collected throughout 3 h at the following discrete intervals: control, 0.017, 0.042, 0.083, 0.25, 0.5, 0.75, 1, 1.5, 2, and 3 h. Eight animals per period were examined.

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Afobazole and M-11 were extracted from the plasma and tissues with diethyl ether. Specimens of the plasma and organ homogenates containing afobasole and M-11 were analyzed by HPLC [1].

Pharmacokinetic parameters were calculated by the simulation independent method.

RESULTS

The distribution of afobazole and M-11 was studied in organs and tissues differing by vascularization degree and in the brain (potential action zone). Afobazole and M-11 were detected in all studied organs and tissues, their distribution being heterogeneous.

The main pharmacokinetic parameters by which these compounds were compared were the area under the pharmacokinetic curve ($AUC_{0-\infty}$), maximum concentration (C_{max}), and half-life period ($T_{1/2el}$) (Table 1).

Analysis of the pharmacokinetic parameters of afobazole and M-11 showed that these compounds are intensely distributed in highly vascularized tissues of the liver, spleen, and kidneys. $AUC_{0-\infty}$ and C_{max} of compound M-11 were significantly higher than those of afobazole. For example, afobazole C_{max} in the plasma was 5.35 μg/ml *vs.* 25.87 μg/ml for M-11, *i.e.* 5-fold higher than afobazole concentration after the same dose of the drug. $AUC_{0-\infty}$ for plasma M-11 7.6

0007-4888/10/1493-0318

TABLE 1. Main Pharmacokinetic Parameters ($AUC_{0-\infty}$, C_{max}, $T_{1/2el}$) of Afobazole and M-11 Metabolite in the Rat Plasma and Organs after a Single Intraperitoneal Injection in a Dose of 25 mg/kg (*M*±*m*)

Organ	Degree of tissue vascularization	Afobazole						M-11 compound		
		Unchanged			M-11 metabolite					
		$AUC_{0-\infty}$, μg/ml×h	C_{max}, μg/ml	$T_{1/2el}$, h	$AUC_{0-\infty}$, μg/ml×h	C_{max}, μg/ml	$T_{1/2el}$, h	$AUC_{0-\infty}$, μg/ml×h	C_{max}, μg/ml	$T_{1/2el}$, h
Plasma		1.66	5.35	0.33	0.42	0.65	0.40	12.58	25.87	0.34
Brain	Target organ	0.97	3.24	0.39	0.33	0.50	0.54	0.55	1.19	0.41
Liver	Intense	4.15	19.83	0.32	2.42	5.51	0.39	15.00	59.62	0.37
Spleen		2.41	19.21	0.39	1.43	2.42	0.46	11.33	47.49	0.31
Kidneys		2.55	8.32	0.38	1.39	2.65	0.44	8.94	28.45	0.39
Muscles	Moderate	1.12	2.99	0.49	0.56	1.02	0.52	4.44	7.67	0.32
Mesentery	Poor	0.35	0.38	0.79	0.24	0.24	0.67	4.53	29.52	0.29

surpassed the corresponding parameter for afobazole. Significantly higher $AUC_{0-\infty}$ and C_{max} values of M-11 compound were observed for all analyzed organs (liver, spleen, kidneys, muscles, and mesentery), except the brain. It seems, that compound M-11 is less subjected to biotransformation than afobazole, and therefore, its $AUC_{0-\infty}$ and C_{max} values were significantly higher in the plasma and all organs, except the brain (Table 1). On the other hand, C_{max} of M-11 in the brain was lower than that of afobazole by 2.7 times, while $AUC_{0-\infty}$ for afobazole in the brain was 1.8 times higher than that of compound M-11.

Similarly as afobazole, compound M-11 is rapidly eliminated from the body, which is seen from $T_{1/2el}$ (Table 1). Only trace concentrations of the analyzed substances were recorded 3 h after intraperitoneal injection.

Hence, compound M-11 is characterized by less pronounced biotransformation than afobazole, more rapid transfer from the central pool (plasma) to the peripheral organs, and lesser penetration into the brain than afobazole.

Estimated $T_{1/2el}$ values indicate that similarly as afobazole, compound M-11 belongs to the group of short-living substances.

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