A MODEL OF THE KINETICS OF BLOOD LEVELS OF PHENAZEPAM AND ITS METABOLITE 3-HYDROXYPHENAZEPAM IN CATS

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Mathematical models in the study of the pharmacokinetics of drugs have recently gained universal recognition [2, 5-7], for they enable pharmacotherapy to be substantially rationalized and optimized, so that the effectiveness of treatment is enhanced. However, besides numerous investigations devoted to models of the kinetics of unchanged preparations, there have been very few studies involving the creation of a combined model of the kinetics of unchanged preparations and their metabolites. The importance of investigations of this kind is evident, for pharmacological activity of a preparation is often due to the action not only of the unchanged preparation itself, but also of its active metabolite.

It was accordingly decided to make a combined study of the kinetics of the tranquilizer phenazepam [7-bromo-1,3-dihydro-5-(2'-chlorophenyl)-2H-1,4-benzodiazepin-2-one] and its pharmacologically active metabolite 3-hydroxyphenazepam [7-bromo-1,3-dihydro-3-hydroxy-5-(2'-chlorophenyl)-2H-1,4-benzodiazepin-2-one] in the blood of cats.

EXPERIMENTAL METHOD

The pharmacokinetics of phenazepam was studied in three male cats weighing 3-4 kg. All the animals received phenazepam internally in a dose of 2 mg/kg in the form of an aqueous suspension with Tween-80. Blood samples were taken from the animals' auricular vein at discrete time intervals for 72 h after administration of the drug. The concentrations of phenazepam and 3-hydroxy-phenazepam in the blood samples were determined by gas chromatography using 63-Ni as electron-capture detector [3]. The kinetics of the unchanged compound was interpreted in the light of a one-chamber model with absorption (Scheme 1, equation 1), whereas the kinetics of 3-hydroxyphenazepam was described in terms of a single one-chamber metabolic model with absorption (Scheme 2, equation 2). The experimental data were analyzed by ADT-4316 computer (Czechoslovakia), using nonlinear regression methods. The following names and abbreviations were used: P) unchanged phenazepam, M) the phenazepam metabolite, 3-hydroxyphenazepam; $C_P(t)$) the blood concentration of P, $C_M(t)$) the blood concentration of M, k_a) absorption constant of the drug, $k_{el,P}$) the overall elimination constant of P, k_f) the constant of formation of M, $k_{el,P'} = k_{el,P} - k_f$, $k_{el,M}$) the overall elimination constant of M, t_{max}) the time taken to reach maximal concentration, V/F) the apparent distribution volume of P, Cl/F) the apparent total clearance of P, and $k_f/k_{el,p}$) the specific contribution of biotransformation of phenazepam into 3-hydroxyphenazepam among all processes of elimination of the drug.

EXPERIMENTAL RESULTS

The kinetic curves of phenazepam and its metabolite 3-hydroxyphenazepam in the blood of cats after internal administration of the compound are shown in Fig. 1, and the calculated parameters of their kinetics are given in Table 1.

Analysis of the results showed differences in the character of the kinetics of unchanged phenazepam in individual animals. For instance, values of k_a in cats Nos. 1 and 3 were an order of magnitude higher than in

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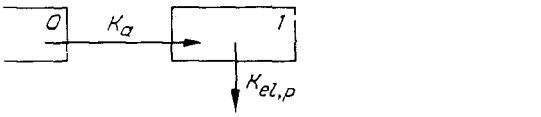
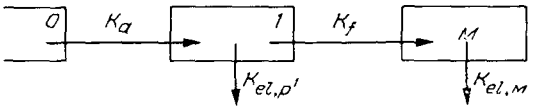


$$C_p(t) = A(e^{-K_{el,p}t} - e^{-K_a t}) \quad (1)$$



$$C_M(t) = A_1 e^{-K_{el,p}t} + A_2 e^{-K_a t} + A_3 e^{-K_{el,M}t} \quad (2)$$

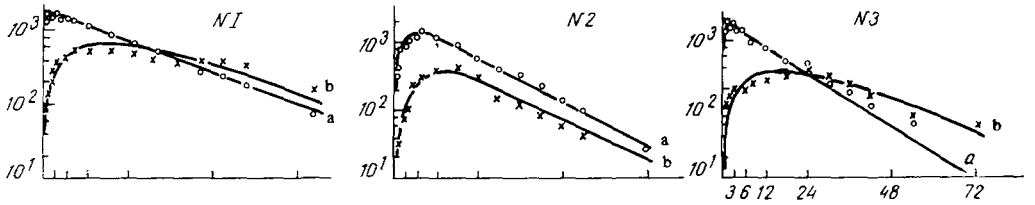


Fig. 1. Kinetic curves of blood levels of phenazepam (a) and 3-hydroxyphenazepam (b) in three cats (Nos. 1, 2, and 3) after administration of phenazepam internally in a dose of 2 mg/kg. Abscissa, time (in h); ordinate, concentrations of phenazepam and 3-hydroxyphenazepam (in ng/ml).

cat No. 2 (Table 1). Individual differences in the rate of elimination of the compound were less marked (the half-elimination time of phenazepam from the cats' blood stream varied from 9.37 to 16.1 h in these animals). Values of V/F were about the same in all the cats.

Besides the unchanged compound, large quantities of 3-hydroxyphenazepam also were recorded in the blood stream (Fig. 1). The phenazepam concentration reached a maximum on average after 3.7 h, whereas the maximum for the metabolite occurred on average after 15.9 h (Table 1). The blood level of 3-hydroxyphenazepam in cats Nos. 1 and 3 24-30 h after administration of the drug, incidentally, was already higher than the concentration of unchanged phenazepam. In its pharmacological activity, 3-hydroxyphenazepam is known to be not inferior to the unchanged compound [1]. It is therefore quite possible that the pharmacological effect of phenazepam in cats may be due partly (especially in the late stages after administration) to the action of the phenazepam metabolite.

Using iterative methods of computer analysis of data for the pharmacokinetics of 3-hydroxyphenazepam within the framework of the metabolic model, parameters of kinetics of the metabolite were calculated (Table 1). Absorption constants (k_a) and also constants of overall elimination of the drug ($k_{el,p}$), calculated independently by two methods – from data for the kinetics of the unchanged compound and data for the kinetics of 3-hydroxyphenazepam (Table 1), had correspondingly close values. This fact confirms the correctness of choice of models describing the kinetics of the unchanged compound and its metabolite.

When the slopes of the kinetic curves of the metabolite and of the compound in the terminal phase (Fig. 1) are compared, the mistaken impression may at first be created that the rate of elimination of the metabolite is higher than the rate of elimination of phenazepam. In reality, as calculation of the kinetics of the metabolite within the constraints of a single metabolic model showed, the elimination constants of the metabolite ($k_{el,M}$) in cats were on average twice as high as the elimination constants of the unchanged compound ($k_{el,p}$). This is in good agreement with a fact known for the benzodiazepines: introduction of a hydroxy group in position 3 of the benzodiazepine molecule increases the polarity of the compound and so accelerates its elimination from the blood [4].

The apparent distribution volume of the metabolite cannot be calculated on the basis of approximation of the experimental data for the kinetics of the metabolite in the blood by theoretical equation 1 (see Scheme 1). However, if it is assumed that the distribution volumes of the metabolite and original compound are equal, several additional parameters of the kinetics of the metabolite can be calculated, and in particular, the constant of formation of the metabolite (k_f) and the specific contribution of biotransformations of the compound into 3-hy-

TABLE 1. Parameters of Kinetics of Phenazepam and 3-Hydroxyphenazepam in Cats after Internal Administration of Phenazepam in a Dose of 2 mg/kg

Parameters of kinetics of	No. of cat	k_a, h^{-1}	$k_{el,P}$, h^{-1}	$k_{el,M}$, h^{-1}	t_{max}, h	V/F, ml/kg	Cl/F, ml/kg/h	k_f, h^{-1}	$\frac{k_f}{k_{el,P}}$
Phenazepam	1	3,05	0,043	—	1,42	1092	47,0	—	—
	2	0,225	0,063	—	7,86	966	60,8	—	—
	3	2,12	0,074	—	1,64	1004	74,3	—	—
	Mean value	1,797	0,060	—	3,64	1021	60,7	—	—
	Standard deviation (%)	1,438	0,016	—	3,66	64,9	13,6	—	—
		(80,0)	(26,7)	—	(100)	(6,33)	(22,4)	—	—
3-hydroxyphenazepam	1	3,0	0,044	0,078	17,18	—	—	0,057	1,30
	2	0,247	0,057	0,199	13,96	—	—	0,058	1,02
	3	2,34	0,067	0,057	16,61	—	—	0,030	0,45
	Mean value	1,861	0,056	0,111	15,92	—	—	0,048	0,92
	Stan. devia. (%)	1,437	0,012	0,077	1,72	—	—	0,016	0,43
	(%)	(77,2)	(21,4)	(69,4)	(10,8)	—	—	(33,3)	(46,7)

Legend. Values of k_f and $k_f/k_{el,P}$ calculated conventionally on the assumption that the distribution volumes of phenazepam (V_P) and its metabolite (V_M) are equal and that hepatovenous accessibility of the metabolite is 1.

droxyphenazepam among all processes of elimination of the drug ($k_f/k_{el,P}$) can be determined. The mean value of $k_f/k_{el,P}$ was 0.92. In other words, on the above assumption, elimination of phenazepam from cats is due to the extent of 92% on average to biotransformation of the unchanged compound into 3-hydroxyphenazepam.

To sum up it can be stated that the use of a combined model of the kinetics of drugs and of their highly active metabolites can broaden the scope for the use of pharmacokinetic methods in clinical practice, for example, in cases when the action not only of a drug, but also of its metabolite, has to be taken into account.

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