Biokinetics of Transdermal Therapeutic Medicinal Form of Phenazepam

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We studied the rate of phenazepam absorption into the blood and its transport to the brain from a transdermal therapeutic system and bioavailability of the drug in this system. Hydrogel matrix consisting of polyvinyl alcohol and 1,2-propylene glycol was used for application. Transdermal application of 0.1-0.4 mg phenazepam in a dose of 14 mg/kg provided a stable level of this drug during application interval (1-48 h), while its bioavailability for blood plasma and brain was 0.63 and 0.2, respectively (determined for 0.4 mg phenazepam). The rate of drug penetration into the blood and brain was 46 and 60 ng/ml/h, respectively.

Key words: *transdermal therapeutic system; phenazepam; bioavailability*

Systemic administration of the drugs via the intact skin is very important because skin is the most available organ in humans. It has large area and extensive capillary net, which are necessary for application and delivery of the drugs to systemic circulation.

The main advantages of transdermal drug administration are prevention of their metabolism in the liver and maintenance of a stable therapeutic level in the organism [3].

Drugs are administered via the skin with the help of transdermal therapeutic systems (TTS), which represent a patch containing bioactive compounds. TTS enable long-term continuous administration (1 day-1 week) of drugs through the skin at a stable rate, which excludes sharp fluctuations of drug concentrations and reduces the risk of side effects often occurring in parenteral and peroral administration [3,6,7].

Phenazepam possessing tranquillizing, anticonvulsant, hypnogenic, and sedative properties and potentiating the effects of anesthetics and analgetics [1] was chosen as the active compound for TTS.

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The aim of the present study was to determine the rate of phenazepam entry into the blood and brain and to estimate its bioavailability under these conditions.

MATERIALS AND METHODS

For transdermal administration of phenazepam we elaborated a hydrogel matrix consisting of polyvinyl alcohol and 1,2-propylene glycol. The matrix produced no irritating or osmotic effects. ^{14}C-Phenazepam was used as the active substance.

Specific activity of ^{4}C-phenazepam was 0.1 Ci/mol (3.7 GBK/mol), radiochromatographic purity was 95.4±2.1%.

Albino random-bread mice weighing 18-23 g were used in the experiments. TTS was applied on shaved skin in the interscapular region. The animals were kept under conditions of free access to food and water, grooming was prevented.

Total radioactivity in the brain was measured on a TRI-CARB 2700 device (Canberra Packard). Brain samples were homogenised with Na_2SO_4 and extracted with chloroform (2×5 ml). Chloroform was evaporated and 8 ml toluene scintillator was added.

The area under the concentration curve (AUC) for ^{4}C-phenazepam in the test objects was determined by

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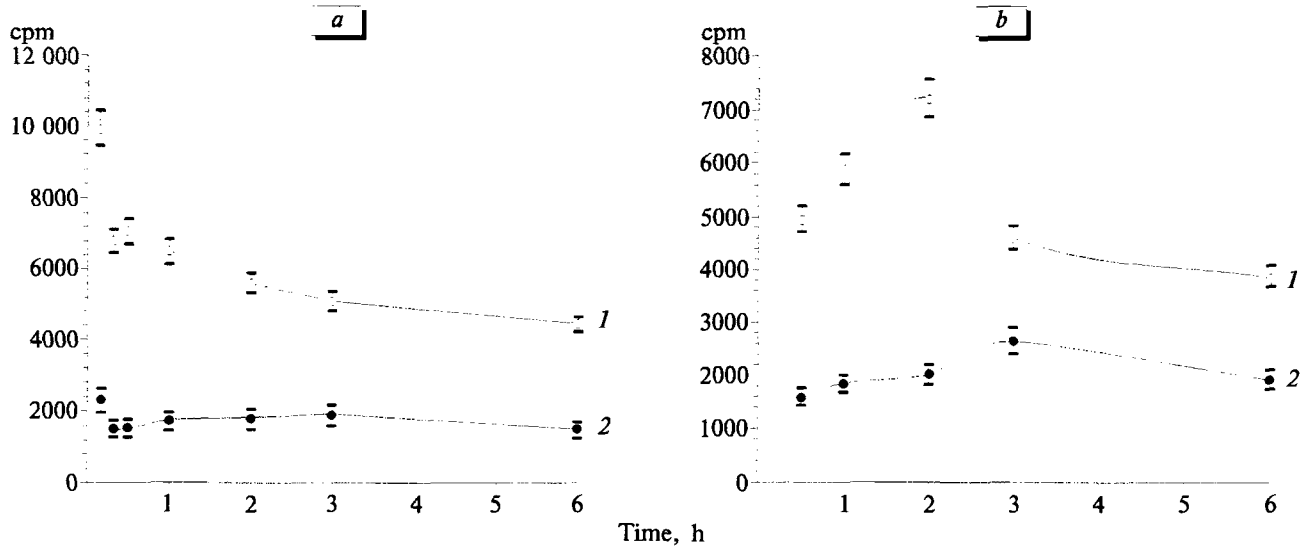

Fig. 1. Concentration of ^{14}C-products in the blood (*1*) and brain (*2*) after intravenous (*a*) and peroral (*b*) application of ^{14}C-phenazepam.

the trapezoid method (within the experimental interval) and as the ratio between elimination constant to the final concentration (end of the curve):

$$AUC_{6-\infty}=C_6/k_{el}$$

where C_6 is the content of ^{14}C-products at the end of examined interval and k_{el} is the elimination constant. Bioavailability of phenazepam was determined by the formula:

$$f=\frac{AUC_{p.o./tr}}{AUC_{i.v.}}\times\frac{D_{i.v.}}{D_{p.o./tr}},$$

where $AUC_{i.v.}$ and $AUC_{p.o./tr}$ are the areas under kinetic curve after intravenous and peroral/transcutaneous application, $D_{i.v.}$ and $D_{p.o./tr}$ are the doses of intravenously or perorally/transcutaneously administered phenazepam, respectively.

The dose of 3-^{14}C-phenazepam for intravenous injections was 14 mg/kg. Transcutaneous application of 0.1, 0.2, and 0.4 mg ^{14}C-phenazepam (3.5, 7.0, and 14.0 mg/kg, respectively) was performed for 48 h.

RESULTS

Before evaluation of ^{14}C-phenazepam bioavailability after transcutaneous application, we examined its distribution in mouse plasma and brain after its intravenous and peroral administration in a dose of 14 mg/kg (Fig. 1, *a, b*). After intravenous injection the content of ^{14}C-products was maximum for the first 10 min of injection and then decreased. These results may be formalized by one-part kinetic scheme, its parameters are presented in Table 1 and Fig. 1.

Our previous studies showed that transcutaneous application of 0.1-0.4 mg ^{14}C-phenazepam produced a rapid anticonvulsive effect: it inhibited tonoclonic convultions and reduced tonic extension of picrotoxin-induced convulsions [2], which attested to a stable level of phenazepam throughout the experiment (48 h).

After increasing the concentration of phenazepam in the applied patch (1 cm^2), AUC in the plasma and

TABLE 1. Pharmacokinetic Parameters of Phenazepam (14 mg/kg) in Mouse Blood and Brain after Intravenous (i/v) and Peroral (p/o) Application

Parameter	Plasma		Brain	
	i/v	p/o	i/v	p/o
C_o, cpm/g	1809	—	7638	—
k_{el}, g×cpm	0.03	—	0.11	—
AUC_{0-6}, cpm×h/g	10,162	12,551	36,359	29,080
$AUC_{0-\infty}$, cpm×h/g	58,762	76,018	76,823	64,044
f	1.0	1.29	1.0	0.83

TABLE 2. Pharmacokinetic Parameters of Phenazepam in the Mouse Blood Plasma and Brain during Transdermal Application

Parameter	Concentration, mg/mouse					
	0.1		0.2		0.4	
	plasma	brain	plasma	brain	plasma	brain
AUC_{0-48}, cpm×h/g	15,382	7762	14,727	8857	21,462	12,678
$AUC_{0-\infty}$, cpm×h/g	24,982	8944	27,227	10,711	42,562	15,569
f	1.49	0.41	0.81	0.28	0.63	0.2

brain increased (Table 2), which indicated decreased bioavailability of the drug.

This can be explained by the formation of skin depot regulating the amount of active compound delivered to the systemic circulation. The increase in the applied phenazepam doses may result only in a longer period of drug release.

The observed characteristic of phenazepam concentration profile after its transcutaneous application cannot be formalized by a linear kinetic scheme. In this case, it is reasonable to use the extreme variant of non-linear kinetic scheme suggesting constant rate of phenazepam delivery to the test objects and subsequent elimination at a constant rate. During the application interval (48 h), the concentration (C_t) changed according to the formula:

$$C_t = \frac{V}{K_{el}}(1-t^{-k_{el}t}),$$

where V is the rate of phenazepam delivery to the tested object.

The rates of phenazepam delivery to the mouse plasma and brain within the experimental interval were 46 and 60 ng/ml/h, respectively.

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