Effect of Lauric Acid on Transdermal Penetration of Phenazepam *In Vivo*

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We studied the effect of lauric acid on transdermal penetration of phenazepam *in vivo*. It was found that treatment with lauric acid 3-fold increased the maximum anticonvulsive effect of phenazepam applied in a transdermal therapeutic system in comparison with the control. Study of the pharmacokinetics of phenazepam transdermal therapeutic system showed its higher bioavailability in the presence of lauric acid (f=0.9).

Key Words: *improvement of permeability; phenazepam; lauric acid*

Creation and studies of transdermal therapeutic systems allowing drug penetration through intact skin for total systemic effect attract now special attention [1]. Optimization of drug therapy is attained via modification of pharmacokinetic parameters of the drug form [2]. If the active drug penetrates through the skin in amounts insufficient for attaining the systemic effect, agents for transdermal administration reversibly increasing permeability of the skin should be applied [4]. Aliphatic acids can be used as agents increasing skin permeability [3,5,6].

The possibility of increasing transdermal penetration of 1,4-benzdiazepine anxiolytic phenazepam is practically interesting, because this drug is widely used for the treatment of chronic neurological diseases, that is, in cases, when the use of transdermal systems is most justified.

The aim of our study was to compare the effect of lauric acid as the agent increasing skin permeability on the pharmacokinetics and pharmacodynamics of transdermal forms of phenazepam.

MATERIALS AND METHODS

Experiments were carried out on random-bred albino mice (18-22 g). Hydrogel transdermal system containing ^{14}C phenazepam (radiochromatographic purity 97.5± 2.4%, activity 3.7×10^{10} Bq, dose 0.4 mg/cm^2) was applied onto shaven skin on the back. The content of lauric acid used for increasing skin permeability in the transdermal therapeutic system (TTS) was 10% (by weight).

Radioactive products in organs and tissues were measured by liquid scintillation photometry. Pharmacological effect of TTS was evaluated by changes in the minimum effective doses of corasole (convulsive agent) inducing clonic tonic convulsions (DCTC) and tonic extension (DTE) in experimental animals after its injection into the caudal vein.

RESULTS

The presence of lauric acid notably modified the pharmacodynamic parameters in comparison with TTS containing no stimulator of transcutaneous permeability (Fig. 1).

After application of TTS containing lauric acid the anticonvulsive effect was recorded as early as 15 min, while after application of standard TTS this effect was recorded only after 2-3 h. The absolute values of the anticonvulsive effect increased approximately 3-fold in comparison with the control. After application of phenazepam TTS without lauric acid this parameter did not exceed 200%. Moreover, the effect of the drug was prolonged to 72 h without appreciable reduction.

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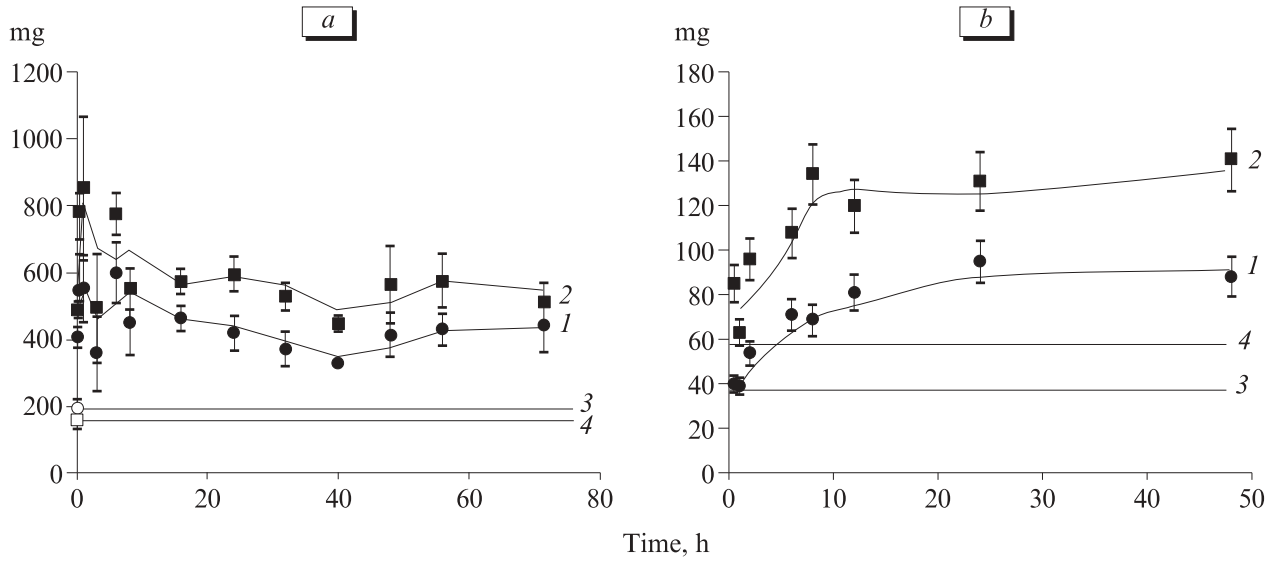

Fig. 1. Changes in the minimum effective doses of corasole after transdermal application of phenazepam (0.4 mg/cm^2, 1 cm^2) in combination with lauric acid (*a*) and without it (*b*). *1*) corasole dose inducing clonic tonic convulsions (DCTC); *2*) corasole dose inducing tonic extension (DTE); *3*) DCTC control; *4*) DTE control.

Pharmacodynamic data were confirmed by measurements of total radioactivity in organs and tissues of experimental animals (Tables 1, 2). For example, two phases of absorption were observed for phenazepam applied in TTS without lauric acid. Phase 1 (rapid) (0-8 h) was characterized by rapid increase in drug concentration in the plasma and brain, while during phase 2 (slow, 12-48 h) the concentrations of ^{14}C products remained at a constant level.

The use of lauric acid as the agent increasing drug penetration through the skin essentially modulated the pharmacokinetic profile of the transdermal phenazepam form. Very rapid increase in plasma and brain concentrations of ^{14}C products is worthy of note, as well as the fact that their concentrations far surpassed the concentrations observed after application of TTS containing no lauric acid. Similar picture was observed in the liver and skin (Table 2).

TABLE 1. Total Radioactivity (cpm) of Mouse Brain after Application of TTS Containing ^{14}C Phenazepam (*M*±*m*, *n*=5)

Time, h	Brain		Blood plasma	
	TTS without lauric acid	TTS with lauric acid	TTS without lauric acid	TTS with lauric acid
0.25	—	256±8	—	140±3
0.5	151±108	298±24	355±165	145±16
1	112±8	654±179	465±145	179±13
2	187±22	—	503±65	—
3	—	1237±138	—	566±126
6	152±37	2162±229	330±21	756±182
8	342±129	2735±265	368±76	1159±90
12	238±42	—	115±15	—
16	—	2495±331	—	1555±234
24	263±50	3252±854	260±100	2110±275
32	—	2218±150	—	1613±69
40	—	1719±368	—	1595±316
48	318±57	1607±332	307±109	1366±97
56	—	1439±442	—	1150±250
72	160±28	947±264	170±22	907±223

Note. Here and in Table 2: "—" — no data.

TABLE 2. Total Radioactivity (cpm) of Mouse Liver and Skin after Application of TTS Containing ^{14}C Phenazepam ($M\pm m$, n=5)

Time, h	Liver		Skin	
	TTS without lauric acid	TTS with lauric acid	TTS without lauric acid	TTS with lauric acid
0.25	78±6	558±101	150±36	26,291±27,53
0.5	90±11	659±46	300±51	17,504±2991
1	420±26	932±43	600±154	14,876±2783
3	1950±213	3121±413	1800±320	18,099±2487
6	816±75	4888±1033	3600±412	23,532±3710
8	1294±96	5789±614	4800±540	27,015±5032
12	2520±184	—	7200±1247	—
16	—	6899±660	—	30,351±1644
24	3180±298	7509±1054	14,400±1526	15,783±3843
32	—	6600±313		13,089±2267
40	—	5964±627	—	6340±1905
48	3396±346	5359±225	28,800±7451	7368±2527
56	—	4940±811	—	5359±1109
72	1256±116	4534±942	15,300±2320	6568±1935

TABLE 3. Pharmacokinetic Parameters of Transdermal Application of ^{14}C Phenazepam as a Component of TTS ($M\pm m$)

Parameter	TTS without lauric acid		TTS with lauric acid	
	blood plasma	brain	blood plasma	brain
Mean retention time, h	19.340±0.564	38.47±2.12	32.69±11.67	32.29±13.40
Mean absorption time, h	13.83±0.57	22.51±2.14	27.18±9.72	16.33±6.62
Absorption constant, h^{-1}	0.072±0.003	0.044±0.004	0.037±0.013	0.063±0.026
Bioavailability	0.379±0.012	0.199±0.013	0.919±0.23	0.833±0.014

Changes in bioavailability (f) of phenazepam applied transdermally can be evaluated by comparing the areas under pharmacokinetic concentration-time curves reflecting drug concentration in the plasma or brain (action biophase) by the formula:

$$f = \frac{AUC_{TD}}{AUC_{VV}} \times \frac{D_{TD}}{D_{VV}},$$

where AUC_{TD} and AUC_{vv} are the areas under pharmacokinetic concentration-time curves after transdermal and intravenous administration of the drug and D_{TD} and D_{vv} are drug doses administered transdermally and intravenously, respectively.

The use of lauric acid as the agent increasing skin permeability significantly (almost 3-4-fold, $p<0.05$) increased bioavailability of transdermal phenazepam form, which was seen from changes in total radioactivity in the plasma and brain (Table 3).

Hence, the use of lauric acid for increasing skin permeability for phenazepam improved bioavailability of its transdermal form, which attested to a significant increase of phenazepam absorption through the skin from the applied matrix.

REFERENCES

1. I. A. Kravchenko, *Transdermal Application of Drugs* [in Russian], Odessa (2001).
2. B. Berner and V. A. John, *Clin. Pharmacokinet.*, **26**, No. 2, 121-134 (1994).
3. U. Bronagh and I. Owen, *Int. J. Pharmaceut.*, **228**, 189-198 (2001).
4. T. K. Ghosh, W. R. Pfister, S. I. Yum, *et al.*, *Transdermal and Topical Drug Delivery Systems*, Buffalo Grove (1997).
5. S. Nicoli, S. Rimondi, P. Colombo, and P. Santi, *Pharm. Res.*, **18**, No. 11, 1634-1637 (2001).
6. T. Ogiso and M. Shintani, *J. Pharm. Sci.*, **79**, 1065 (1990).