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Percutaneous absorption of azidothymidine in rats

Toshinobu Seki, Takeo Kawaguchi, Kenji Sugibayashi, Kazuhiko Juni and Yasunori Morimoto

Faculty of Pharmaceutical Sciences, Josai University, Sakado (Japan)

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Summary

Percutaneous absorption of azidothymidine (AZT) was examined in rats. When AZT was applied as a solution in 10% oleic acid/water on the abdominal skin which had been treated with 10% oleic acid/water for 24 h, considerable plasma concentrations of AZT were observed.

Azidothymidine (Zidovudine, AZT) is a strong inhibitor of the reverse transcriptase isolated from acquired immunodeficiency syndrome (AIDS) virus, and has clinical activity in patients with AIDS or AIDS-related complex by oral administrations. Orally administered AZT, however, has strong side effects, especially on the bone marrow (Mir and Costello, 1988), and the oral preparation must be administered every 4 h to keep the effective AZT concentration in plasma (Klecker et al., 1987; Dournon et al., 1988). Since AZT acts as a metabolic antagonist of thymidine, the anti-viral effect of AZT can be time-dependent. Therefore, an adequate zero-order delivery of AZT is desired to maintain expected anti-AIDS effect and to avoid the strong side effects which may be attributed to an exceeded plasma level of AZT immediately after an intravenous or oral administration.

Correspondence: T. Seki, Faculty of Pharmaceutical Sciences, Josai University, 1-1 Keyakidai, Sakado, Saitama 350-02, Japan.

The skin is often very helpful as an administration site to maintain suitable plasma concentration of drugs (Chien, 1987). Percutaneous application of AZT could be useful to improve anti-AIDS effect and patient compliance and to avoid the side effects.

In the present study, percutaneous absorption of AZT was examined in rats. A male Wistar rat (200 g), whose abdominal hair had been removed by a barber's clippers, was anesthetized with urethane. A test solution containing 5 mg of AZT (in 1 ml, 25 mg/kg) was applied on an area of 4.9 cm^2 by using a cylindrical glass cell fixed on the abdominal skin by an adhesive agent. A 100 μl of plasma was collected at specified time after the application. In order to compare the transdermal systems with a conventional oral dosage form, a 0.5 ml of AZT solution (3 mg/kg) was administered orally. The plasma concentrations of AZT were determined by using a reversed-phase HPLC system and are shown in Table 1. Conditions for the HPLC were as follows: column, 4.6 mm × 250 mm stainless column packed with Nucleosil $5C_{18}$;

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TABLE 1

Plasma concentration of AZT after oral or percutaneous applications of AZT

	Plasma concentration of AZT (μM)							
	Time (h)							
	0.5	1	2	4	6	8	23	24
p.o. (3 mg/kg)	3.1 ± 0.4	2.5 ± 0.3	0.5 ± 0.2	0.2 ± 0.0	n.d.	n.d.	–	n.d.
p.c. (25 mg/kg) vehicle:								
water	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	–	n.d.
IPM	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	–	n.d.
10% MP	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
10% OA	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	1.1 ± 0.8	1.4 ± 0.9
10% OA in pretreated rat with 10% OA	0.2 ± 0.1	0.6 ± 0.3	0.7 ± 0.3	1.5 ± 0.7	1.5 ± 0.4	1.5 ± 0.2	– [a]	– [a]

p.o., oral administration; p.c., percutaneous administration; n.d., not detected (< 0.1 μM).

[a] Not done, since the pretreated rats were suppressed for 24 h before the drug application, we considered that continuation of the experiments was cruel to the animals.

Data are the mean ± S.E. ($n = 3$).

mobile phase, 15% acetonitrile containing 0.1% acetic acid; detector, UV 265 nm; flow rate, 1 ml/min.

The plasma concentration-time profile of AZT after oral administration in rats is similar to that in patients with AIDS reported by Klecker et al. (1987). Since the plasma level of AZT following application on the skin in the simple water system was too low to be detected, isopropyl myristate (IPM), *N*-methyl-2-pyrrolidone (MP) and oleic acid (OA), these agents have been permitted as additives for external preparations, were used as penetration enhancers (Barry and Bennett, 1987; Sato et al., 1988; Sugibayashi et al., 1988; Yamada and Uda, 1987; Seki et al., 1989). Since the solubilities of IPM and OA in water are small, 10% preparations with these additives were applied as emulsions. Although the plasma concentration of AZT after the application of IPM or 10% MP aqueous solution was also undetectable during the experimental period (24 h), considerable plasma concentrations of AZT were detected with the 10% OA system (1.1 and 1.4 μM at 23 and 24 h, respectively). In order to ascertain the enhancing effect of OA, we used the pretreated rats whose abdominal skin had been treated with drug-free 10% OA for 24 h before the drug application. In the pretreated rats, the plasma concentration of AZT following 10% OA application was well above the detection limit (0.1 μM) even at 0.5 h after the application. These results suggest that the permeability of AZT through the skin, which should affect the plasma level of AZT after percutaneous applications, can be improved by the use of penetration enhancers such as OA.

Based on the in vitro pharmacodynamic studies with HTLV-III/LAV (Mitsuya et al., 1985), Klecker et al. (1987) had reported that the plasma concentration of AZT required to expect a therapeutic effect is achieved at a dose of 5 mg/kg given intravenously every 4 h. In the present study, considerable plasma concentrations of AZT were obtained (0.6–1.5 μM) after percutaneous application of the 10% OA system in the pretreated rats. By overcoming the many problems related with animal scale-up on the skin permeation of AZT (Sato et al., 1989), the transdermal delivery system of AZT could be useful for AIDS therapy. A search for more effective enhancers, examination of permeability of ester derivative of AZT and evaluation of their simultaneous use are under way in our laboratory.

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