International Journal of Pharmaceutics, 77 (1991) 71–74

ADONIS 037851739100369B

IJP 02560

Notes

Rectal absorption of Zidovudine

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(Received 7 March 1991)
(Modified version received 15 May 1991)
(Accepted 1 July 1991)

Key words: Zidovudine; Rectal absorption; Hydroxypropyl cellulose

Summary

Rectal absorption of Zidovudine (3′-azido-3′-deoxythymidine, AZT) was investigated in order to determine the feasibility of developing AZT suppositories. Although the small intestine shows a higher absorption rate than the stomach and large intestine in rats, considerable absorption of AZT was observed from the lower large intestine (8 cm above the anus). A sustained-release suppository was prepared by direct compression of hydroxypropyl cellulose (HPC) with AZT. During in vivo experiments in rats, this suppository (10 mg or 37.5 μmol AZT/kg) maintained constant plasma levels above 1 μM for more than 6 h. The results suggest that suppositories can prove useful as an alternative dosage form of AZT administration.

3′-Azido-3′-deoxythymidine (AZT or Zidovudine), an inhibitor of the reverse transcriptase of the human immunodeficiency virus (HIV), has demonstrated clinical benefit mostly by oral administration in the management of syndromes (AIDS and ARC) associated with the HIV infection. Although orally administered AZT is rapidly absorbed, considerable first-pass losses (> 40%) and rapid elimination (a half-life of 1 h) (Klecker et al., 1987) necessitate a high daily dose and frequent administration (5–10 mg/kg, every 4 h). In addition, AZT has produced dose-limiting bone marrow toxicities (Dournon et al., 1988; Mir and Costello, 1988), which may be attributable to an excessive plasma concentration of the substance immediately following oral administration. In an attempt to overcome these drawbacks, prodrugs (Aggarwal et al., 1990; Hostetler et al., 1990; Kawaguchi et al., 1990, 1991), probenecid combination (Hedaya and Sawchuk, 1989; Hedaya et al., 1990), pump delivery (Gallo et al., 1989) and transdermal delivery systems (Seki et al., 1990a,b; Wearley and Chien, 1990) have been investigated. The rectal lumen has been recognized as a promising route for administration in order to avoid first-pass effects, and the usefulness of sustained-release suppositories for reducing the frequency of drug administration has also been reported (Nishihata et al., 1986; Huang et al., 1987; Nakajima et al., 1987). The objective of this study was to investigate the rectal absorption of AZT in order to evaluate the feasibility of developing an AZT suppository to increase bioavailability and/or decrease the frequency of dosing and reduce side effects.

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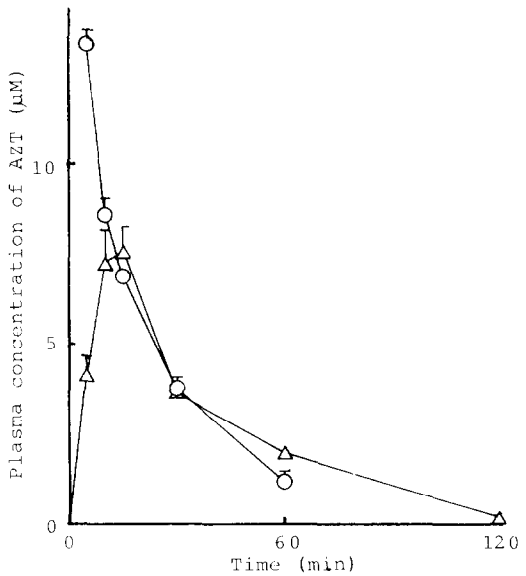

Fig. 1. Plasma concentration-time profile following i.v. (3 mg/kg, ○) and p.o. (3 mg/kg, △) administration to rats ($n = 3$).

To obtain pharmacokinetic data, AZT (3 mg or 11.2 μmol/kg) was orally (2.5 ml/kg of water solution) or intravenously (1.0 ml/kg of saline solution) administered to unanesthetized Wistar rats (male, 190–250 g), and the plasma concentrations were determined according to the method reported previously (Kawaguchi et al., 1990). The time-concentration profiles in Fig. 1 show rapid absorption from the gastrointestinal tract (T_{max} = 15 min) and a short half-life ($k_{el} = 2.8 \pm 0.4$ h^{-1}, mean $T_{1/2} = 0.25$ h, $V_d = 0.75 \pm 0.03$ l/kg) in the body. Since AZT is a thymidine analogue, the nucleoside-specific transport mechanism, which is often accompanied by site-specific absorption, might be partly responsible for its rapid absorption from the gastrointestinal tract. Therefore, loop experiments were carried out for the evaluation of absorption rates from the stomach, upper small intestine (8 cm from the pylorus), lower small intestine (8 cm above the appendix), upper large intestine (8 cm from the appendix), and lower large intestine (8 cm above the anus). Rats were anesthetized with sodium pentobarbital (50 mg/kg, i.p.) and a single loop was prepared according to the method of Levine and Pelikan (1961). After washing the loop with 10 ml of saline, 0.5 ml of drug solution (2.25 M) was injected into the loop. The loop was removed 30 min after the application, and the contents were emptied into a 10 ml flask. The mucosal side of the loop was rinsed with saline to give a volume of 10 ml. The samples were analyzed by HPLC. Table 1 lists the percentages of AZT remaining in each region. Although the high degree of absorption from the small intestinal region was not unexpected, considerable absorption was also observed in the large intestines. Since the enzymatic degradation of AZT was observed in homogenates of the large intestines (data not shown), the above result would seem to support the rationality for developing suppositories containing AZT.

Since hydroxypropyl cellulose (HPC) has been investigated in detail as a polymer matrix for sustained release dosage forms (Machida and Nagai, 1978; Machida et al., 1979), a directly compressed HPC tablet (prepared by using SSP-10, Simadzu Kinzoku Co.) was employed as the sustained-release suppository. HPC (150–400 cps, Wako Pure Chemical Co., Tokyo) and AZT (10 or 20% w/w) were mixed and compressed at 200 kg/cm^2 for 5 min to form a thin tablet (∅ 5.0 mm). For preparation of a conventional suppository, glyceride base (Witepsol H-15, Dynamite-Nobel, Germany) and AZT (1% w/w) were mixed at 50 °C. The molten mixture was poured into a polyethylene tube (4.8 mm i.d.) and allowed to stand at room temperature for at least 24 h. Release experiments were carried out according to the method reported by Kakemi et al. (1967). Briefly, each suppository containing 2 mg AZT (200 mg for conventional suppository, 10 and 20 mg for HPC tablets containing 20 and 10% AZT, respectively) was placed on a piece of cylindrical filter paper (No. 84, 30 × 100 mm, Advantec Co., Tokyo). The top of the filter paper (5 mm) was immersed in saline (50 ml) stirred at 37 °C. 0.5 ml of the saline was withdrawn periodically and the same volume of fresh saline was added. Samples were analyzed by HPLC. Fig. 2 shows the release profiles of the suppositories; sustained and relatively constant release was achieved in the suppositories formed by the direct compression of

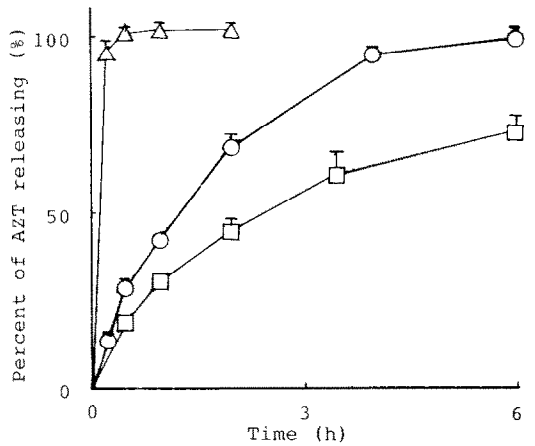

Fig. 2. Release profiles of AZT suppositories. Witepsol (△), hydroxypropyl cellulose containing 20% AZT (○), and hydroxypropyl cellulose containing 10% AZT (□).

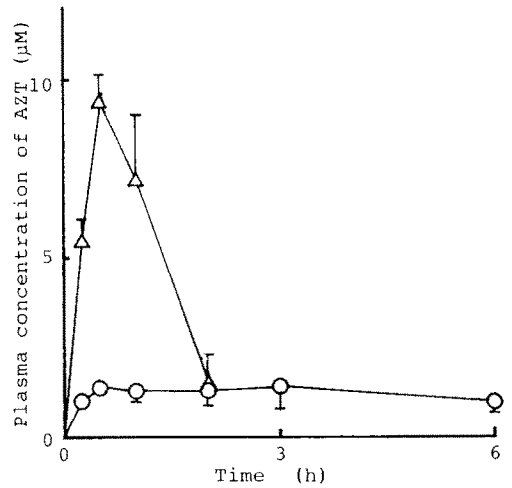

Fig. 3. Plasma concentration-time profiles following the administration of AZT suppositories: conventional (△), sustained-release (○).

HPC. The suppository with a higher HPC content (containing 10% AZT, □) showed slower release than that of lower HPC content (containing 20% AZT, ○). Since high drug content suppositories may be preferable because of the high clinical dose of AZT as cited above, the higher content suppository (20% AZT) was used for the following in vivo experiment.

Rectal absorption of AZT from the suppositories was evaluated in rats. A suppository (10 mg AZT/kg) was inserted into each of three male Wistar rats (180–220 g), and the anus was closed with an adhesive agent to prevent leakage. The animals were placed in individual Bollman cages and deprived of food but were allowed water ad libitum. Blood samples (0.25 ml/sample, 2 ml total) were collected from an artery through a previously implanted (at least 20 h before the study) carotid catheter. The blood was centrifuged and the resulting supernatant was analyzed by HPLC as reported previously (Kawaguchi et al., 1990). Fig. 3 illustrates the plasma concentration-time profiles following administration of the sustained-release (○) and conventional form (△). While AZT was absorbed rapidly (T_{max} = 30 min) from the conventional suppository and eliminated within 3 h, the plasma levels following administration of the sustained-release suppository remained high, a concentration greater than 1 μM, the supposed minimum level for an antiviral effect (Klecker et al., 1987) being maintained over 6 h. The area under the blood concentration-time curve (AUC) following each administration was calculated by the trapezoidal rule and the results are compared in Table 2. Although the AUC following oral administration was higher than that of the suppositories, it should be noted that the first-pass effect (glucuronization) was observed only in human and simians. Since the AUC of the sustained-release suppository was calculated only from the findings at 6 h and the elimination constant (k_{el}, obtained from i.v. data), the value corresponds to the amount of AZT absorbed by that time and the true bioavailability of the suppository may be even greater.

TABLE 1

AZT absorption from stomach and intestines

Region	Length (cm)	Volume (ml)	AZT remaining (% ± SE, n = 3)
Stomach	–	0.5	45.9 ± 1.2
Upper small	8.0	0.5	18.9 ± 2.0
Lower small	8.0	0.5	19.0 ± 5.0
Upper large	8.0	0.5	57.8 ± 7.1
Lower large	8.0	0.5	52.2 ± 6.0

TABLE 2

AUC of AZT following i.v., p.o. and rectal administration

Administration	AUC (μM h $\pm$ SE, $n = 3$)	Mean AUC/dose (h kg l^{-1})
i.v. (11.2 μmol/kg)	6.07 $\pm$ 0.43	0.54
p.o. (11.2 μmol/kg)	5.29 + 0.10	0.47
Rectal (37.5 μmol/kg) (conventional)	12.38 $\pm$ 2.63	0.33
Rectal (37.5 μmol/kg) (sustained-release)	7.30 $\pm$ 2.54	0.19

In conclusion, suppositories can be an alternative dosage form of AZT administration, and this sustained-release form may decrease the administration frequency necessary and/or reduce side-effects.

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