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The effect of fatty acids on the rectal absorption of acyclovir in rats

MASARU YAMAZAKI, SOICHI ITOH, MASAYOSHI SAWANOI, MIKI KOBAYASHI, SAYAKA SUZUKI, TOSHIAKI KOMATSU*, KAZUHISA TANABE†, *Faculty of Pharmaceutical Sciences, Osaka University, 1–6, Yamadaoka, Suita, Osaka 565, Japan, * Nippon Wellcome Co. Ltd, 1–14 Miyahara 4-chome, Yodogawa-ku, Osaka 532 Japan and † Department of Pharmacy, Osaka University Hospital, 1-1-50 Fukushima, Fukushimaku, Osaka 553, Japan*

Abstract—The enhancing effect of fatty acids on the rectal absorption of acyclovir has been evaluated in rats. Acyclovir proved to be absorbed to the extent of 3 to 9% after oral administration. After rectal administration in the absence of absorption-promoter, the bioavailability of acyclovir was 37%. Its rectal administration with 4% sodium caprate resulted in enhanced bioavailability (81 ± 3%).

Acyclovir, 9-(2-hydroxyethoxymethyl)guanine, an agent active against many herpes viruses, is incompletely absorbed after oral administration with an estimated bioavailability in man of about 20% from 200 mg single doses (de Miranda & Blum 1983). The normal frequency of dosing is every 4 h.

The object of this study was to investigate the rectal absorption of acyclovir to establish whether it might be a means of increasing bioavailability and/or of decreasing the frequency of dosing. Antibiotics are generally not well absorbed from the rectum, but some have been formulated as suppositories, using various sodium salts of fatty acids as adjuvants, to enhance rectal absorption (Nishimura et al 1985). The present report describes the effect of sodium salts of fatty acids on the rectal absorption of acyclovir in rats.

Materials and methods

Chemicals. Acyclovir (Zovirax for intravenous infusion, freeze-dried product) was supplied by Nippon Wellcome Company Ltd, Osaka, Japan. Triglyceride suppository base, Pharmasol B115, and macrogol 4000 were gifts from Nippon Oil & Fat Company, Tokyo, Japan. Sodium salts of caproic acid, caprylic acid, capric acid and lauric acid were purchased from Ishizu Pharmaceutical Company, Osaka, Japan. All other reagents were of analytical grade.

Preparation of acyclovir suppository. For the preparation of suppositories, the triglyceride base and acyclovir were mixed with or without the sodium salts of fatty acids at 40 °C. The molten mixture was poured into a polythene tube (4 mm i.d.) and kept in a refrigerator for at least 24 h. The acyclovir content was 100 mg g^{-1} of suppository. Macrogol base was melted at 60 °C.

Animal experiments. Male Wistar rats, 230–250 g, were used. They were fasted but allowed free access to water. The dose of acyclovir was 40 mg kg^{-1} in all experiments. Rats were anaesthetized with pentobarbitone (40 mg kg^{-1}), and body temperature was maintained at 37 °C using a temperature-controlled box. Acyclovir was dissolved in 0·24 mL of isotonic sodium chloride solution, and infused intravenously into the right jugular vein for 60 min. For oral administration, the drug solution (16 mg mL^{-1}) was administered via a stomach tube. For duodenal administration, the duodenum was exposed through an incision in the upper half of the midline and acyclovir solution (16 mg mL^{-1}) injected intraduodenally. For rectal administration, the suppository was inserted. Microenema (0·24 mL) was administered through tubing to a depth of 1 cm from the outer rectal sphincter, and the anus closed with an adhesive agent to prevent leakage. Blood samples of 0·2 mL were taken from a cannulated femoral artery at designated times, and centrifuged at 3000 rev min^{-1} for 10 min to prepare the plasma.

Correspondence to: M. Yamazaki, Faculty of Pharmaceutical Sciences, Osaka University, 1 6 Yamadaoka, Suita, Osaka 565, Japan.

Assay method. Acyclovir in plasma was measured by a modification of the HPLC method of Land & Bye (1981), under the following conditions: Develosil ODS-5 column material (Nomura Chemical Company, Aichi, Japan) with a column length of 15 cm (4 mm i.d.): the mobile phase was 5 mM acetate buffer pH 4·0 containing 5 mM sodium octanesulphonate and 5 mM sodium perchlorate. A JASCO Model 880PU high performance liquid chromatograph fitted with a JASCO UVIDEC-100 detector at 250 nm was used.

Pharmacokinetic analysis. The plasma acyclovir concentration-time curve after intravenous infusion was fitted to biphasic kinetics by a non-linear least-squares regression computer program, MULTI (Yamaoka et al 1981). The areas under the plasma concentration-time curves from 0 to 3 h ($AUC_{0\ 3}$) were calculated using the trapezoidal rule. Relative bioavailabilities (F) were calculated as $[AUC_{0\ 3}]/[AUC_{0\ 3}]_{iv}$, where $[AUC_{0\ 3}]_{iv}$ is the AUC after intravenous infusion and $[AUC_{0\ 3}]$ is the AUC after other administrations. The apparent half-lives were determined by a linear regression analysis of the logarithmic concentration versus time data. The parameters were calculated for each animal, and then the means and standard errors for the parameters were calculated.

Release of acyclovir from suppositories. The rates of release of acyclovir from the suppositories at 37 °C were measured by the method of Itoh (1987) using a dialysis membrane (Visking cellulose tubing, 20/32″, Union Carbide Co., USA). Samples were withdrawn from the beaker at designated intervals and the amount of acyclovir released was determined by UV spectrophotometry.

Results and discussion

Fig. 1 shows the mean plasma concentration-time profiles after intravenous, oral and rectal administration of acyclovir. The plasma concentration after the completion of a 1 h constant rate infusion decreased rapidly. The disappearance followed a bi-exponential curve, and the disappearance half-lives of the α- and β-phases were 0·18 and 2·35 h, respectively. Oral administration of acyclovir resulted in a significantly lower plasma concentration with a peak of 1·8 ± 0·4 μg mL^{-1}, and the bioavailability compared with intravenous infusion over the time 0–3 h was about 6%. This is much lower than that reported in man (de Miranda & Blum 1983).

Duodenal absorption was relatively fast with maximum plasma concentration at 5–10 min. However, the difference between $AUC_{0\ 3}$ in the case of oral and duodenal administration was not significant (Table 1). This suggests that the poor oral absorption in rat is not due to degradation of acyclovir in the stomach. Lewis et al (1986) have reported that improved absorption of acyclovir in man could not be obtained by bypassing the stomach.

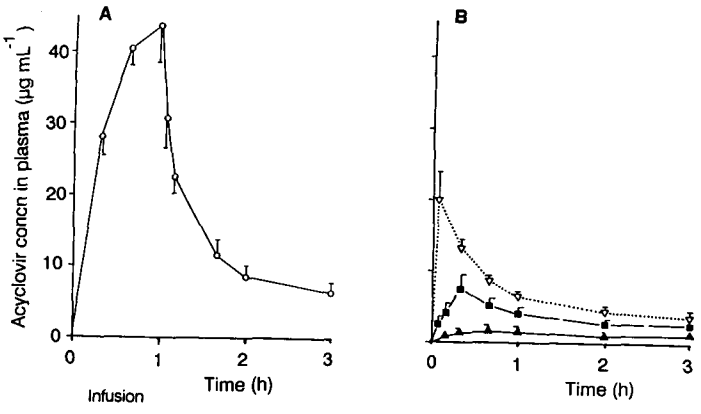

FIG. 1. Plasma acyclovir concentration (mean ± s.e.) in rats after intravenous infusion (○, n = 5) (A), oral (▲, n = 7) and rectal (triglyceride base, ▽, n = 7; macrogol base, ■, n = 7) administration (B). Dose 40 mg kg^{-1}.

Rectal absorption from the macrogol base suppository was slower, with maximum plasma concentrations at 20 min. The amount absorbed was higher than by oral administration (Fig. 1).

Rectal absorption from microenema resulted in a rapid increase of plasma concentration, but the maximum plasma concentration and $AUC_{0\,3}$ were similar to that observed after administration of the macrogol base suppository (Table 1).

Much higher plasma concentrations were achieved from the triglyceride base suppository; and the maximum plasma concentration was attained within 5 min (Fig. 1). The data show an 11-fold improvement in the maximum plasma concentrations compared with those obtained after oral administration. Bioavailability (37%) was 5·7 times that with oral administration (Table 1).

The addition of 4% sodium caprylate, sodium caprate or sodium laurate increased bioavailability by 62, 119 and 54%, respectively, compared with values for bioavailability without fatty acids (Table 1). The effect of 4% sodium caproate was not significant ($P > 0{\cdot}05$).

Fig. 2 and Table 1 show the effect of varying concentrations of fatty acids on the absorption of acyclovir. Plasma acyclovir concentrations increased rapidly and reached a maximum at about 5 min after rectal administration in the presence of sodium caprylate (Fig. 2). However, it is also apparent from Fig. 2 that the AUC values were roughly similar to those obtained following rectal administration without adjuvant, although the inclusion of 4% of sodium caprylate increased the bioavailability of acyclovir.

After rectal administration of acyclovir in the presence of sodium caprate, the plasma concentration increased rapidly, reaching a maximum concentration 5–10 min after administration (Fig. 2). The high plasma concentration was long-lived. The presence of 1% sodium caprate hardly enhanced rectal absorption of acyclovir. The addition of 4% of sodium caprate to the suppository resulted in an average bioavailability of 80·9 ± 2·5%. However, the addition of 2 or 6% sodium caprate produced a lower AUC for acyclovir. Mishima et al (1987) demonstrated that the optimum concentration of sodium caprate as an insulin absorption promoter on rat nasal cavity was 1–2%. In this study we obtained best results with the 4% concentration.

The administration of a suppository containing 4 and 6% sodium laurate caused an increase in rectal absorption whereas 1 and 2% did not (Fig. 2).

Of all sodium salts of fatty acids examined, the enhancing

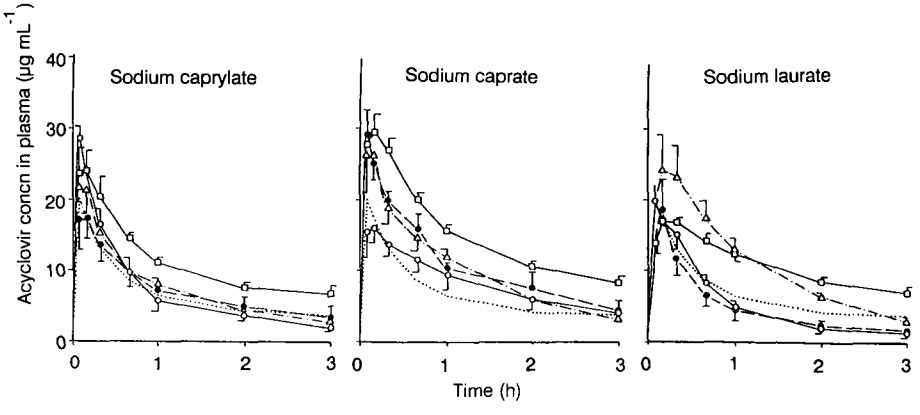

FIG. 2. Effect of sodium salts of fatty acids on the rectal absorption of acylovir in rats. Dose 40 mg kg^{-1}. Each value is the mean ± s.e. of 6–8 experiments. Key: control from Fig. 1 (· · · · ·); 1% (○), 2% (●), 4% (□) and 6% (△) sodium salt as indicated.

Table 1. Maximum concentration (C_{max}) in plasma, time of maximum concentration (T_{max}), AUC_{0-3}, bioavailabilities (F) and apparent half-life ($t_{\frac{1}{2}}$) of 40 mg kg^{-1} dose of acyclovir in rats. n = number of animals.

Administration			n	C_{max} ± s.e. ($\mu g\ mL^{-1}$)	T_{max} (min)	AUC_{0-3} ± s.e. ($\mu g\ mL^{-1}\ h$)	F	Apparent $t_{\frac{1}{2}}$ ± s.e. (h)
Intravenous infusion			5	43·8 ± 5·3	60	55·1 ± 5·4	1·00	0·18 ± 0·02
Oral administration			7	1·8 ± 0·4	40–60	3·6 ± 1·0	0·06	2·68 ± 0·70
Duodenal administration			4	5·1 ± 0·5	5–10	5·1 ± 1·2	0·09	0·20 ± 0·08
Rectal administration								
Base	Adjuvant (%)							
(Solution)	None		3	7·4 ± 1·5	5–10	15·9 ± 3·5	0·29	0·65 ± 0·11
Macrogol	None		7	7·5 ± 2·1	20	11·0 ± 3·3	0·20	0·64 ± 0·07
Triglyceride	None		7	20·2 ± 4·2	5	20·6 ± 1·1	0·37	0·59 ± 0·07
Triglyceride	Na caproate	(4)	6	22·1 ± 4·3	5	24·0 ± 3·7	0·44	0·34 ± 0·04
Triglyceride	Na caprylate	(1)	6	28·7 ± 1·9	5	21·4 ± 3·4	0·39	0·38 ± 0·06
Triglyceride	Na caprylate	(2)	6	17·2 ± 2·8	5–10	21·7 ± 5·4	0·39	0·42 ± 0·01
Triglyceride	Na caprylate	(4)	8	24·0 ± 3·0	5–10	33·3 ± 1·2*	0·60	0·63 ± 0·12
Triglyceride	Na caprylate	(6)	6	21·6 ± 4·1	5–10	23·1 ± 3·4	0·42	0·45 ± 0·01
Triglyceride	Na caprate	(1)	6	16·1 ± 2·0	5–10	24·9 ± 4·4	0·45	0·63 ± 0·24
Triglyceride	Na caprate	(2)	6	29·2 ± 4·7	5	32·6 ± 5·9*	0·59	0·51 ± 0·02
Triglyceride	Na caprate	(4)	8	29·6 ± 2·7	10	44·6 ± 1·4**	0·81	0·95 ± 0·13
Triglyceride	Na caprate	(6)	6	26·4 ± 5·0	5–10	30·7 ± 3·4*	0·56	0·71 ± 0·12
Triglyceride	Na laurate	(1)	6	20·2 ± 2·4	5	16·1 ± 1·8	0·29	0·42 ± 0·05
Triglyceride	Na laurate	(2)	6	18·7 ± 5·7	10	14·6 ± 3·6	0·26	0·45 ± 0·07
Triglyceride	Na laurate	(4)	7	17·1 ± 0·8	10–20	31·6 ± 2·0*	0·57	1·04 ± 0·09
Triglyceride	Na laurate	(6)	6	24·3 ± 6·2	10	33·0 ± 4·8*	0·60	0·89 ± 0·14

* $P < 0·05$, ** $P < 0·01$ compared with the value of triglyceride base without adjuvant.

action of 4% of sodium caprate appeared to be the strongest, as shown by the bioavailability figures (Table 1). Attainment of a higher plasma concentration after administration of acyclovir suppositories containing sodium salts of fatty acids was not always obtained, but this may be desirable. The rate of elimination following maximum concentration is prolonged after rectal administration because the absorption process is protracted (Table 1). Thus, high concentrations are maintained for a longer period after the rectal administrations than after the intravenous infusion.

To explore the possible absorption-enhancing mechanisms of these adjuvants, we studied the release of acyclovir from suppositories into water buffered at pH 7·0. Acyclovir was inadequately released from the base without adjuvant (Fig. 3). For the suppositories containing fatty acids, the amount of acyclovir released was ~ 100%, irrespective of the nature of the fatty acid (Fig. 3) or its concentration in the range 1–6% (not shown). The adjuvants appear to improve the release of acyclovir from the bases.

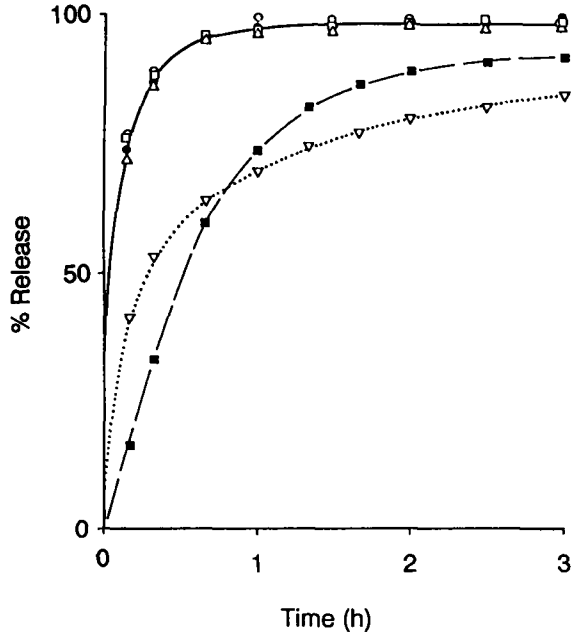

FIG. 3. Release profiles of acyclovir from different suppository bases into a phosphate buffer (pH 7·0). Key: macrogol (■); triglyceride (▽); triglyceride containing 4% sodium caproate (○), sodium caprylate (●), sodium caprate (□) and sodium laurate (△).

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