J. Pharm. Pharmacol. 1991, 43: 465–469
Received October 15, 1990

Effect of Age on the Gastrointestinal Absorption of Acyclovir in Rats

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Abstract—Drug elimination from the body after intravenous administration of acyclovir (20 mg kg^{-1}) was delayed in 1-week-old rats but the pharmacokinetic data for 2·5-week-old rats were the same as those for 8-week-old rats. The areas under the plasma concentration-time curves at 0–∞ h (AUC) after oral administration of acyclovir (20 mg kg^{-1}) decreased with increasing age. The absolute bioavailabilities for 1-, 2·5-, 3- and 8-week-old rats were 77·59, 51·52, 14·61 and 7·30%, respectively. The gastrointestinal absorption of poorly absorbed acyclovir was good for rats younger than 2·5 weeks but dropped abruptly between 2·5 and 3 weeks of age. The intestinal membrane permeability of acyclovir was studied using the everted sac method. The rate of transfer of an initial concentration of 10 μM acyclovir from the mucosal to the serosal side was constant until 60 min in rats of different ages while the rate in 2·5-week-old rats was significantly greater than that in 3-, 4- and 8-week-old rats. Abrupt in-vivo and in-vitro changes were observed in the experimental results between 2·5- and 3-week-old rats; this period coincided with the weaning period of the rat. The membrane transport mechanism of acyclovir in 2·5- and 8-week-old rats was also studied. Cumulative transferred amounts of acyclovir were linear ($r = 0·99$) over the range 5 μM–1 mM and dose-independent. The influence of metabolic inhibitors (sodium azide, 2,4-dinitrophenol, ouabain), purine and pyrimidine analogues (2-deoxyguanosine, guanine, adenine, uridine) and temperature on the permeation of acyclovir was studied. The permeation of acyclovir was inhibited only by 2-deoxyguanosine and guanine in 2·5-week-old rats. These results suggest that throughout the maturation period, the gastrointestinal absorption mechanism of acyclovir is predominantly via passive diffusion with little or no active or facilitated transport. The abrupt change that occurs during the weaning period is attributable not to facilitated transport but to a change in the factors regarding passive transport.

Acyclovir, 9-(2-hydroxyethoxy methyl) guanine, is an active agent against many herpes viruses (Schaeffer et al 1978). It is virtually non-toxic to man if its renal tubular concentration is not allowed to rise too high, as can happen in the case of urinary obstruction. Thus, acyclovir can be an effective chemotherapeutic agent. However, it is not very soluble in water (solubility, 0·13%) or oil (solubility in octanol, 0·1%), and the octanol/water partition coefficient is 0·018. Thus, incomplete gastrointestinal absorption and short-lived peak plasma concentrations have been found after oral dosing of acyclovir to treat herpes simplex (Rogers & Fowle 1983). The estimated absolute bioavailability of acyclovir in man is between 15 and 30% (Straus et al 1983). Capacity-limited absorption described may account for the poor absorption; the amount of absorption after oral administration in dogs did not increase linearly with the dose (de Miranda & Blum 1983). Lewis et al (1986) reported that the limitation of gastrointestinal absorption may be due to limited solubility, a small absorption window or carrier-mediated transport. Other compounds having the purine or pyrimidine skeleton, fluorouracil (Smith et al 1988) and mercaptopurine (Sasaki et al 1986) have gastrointestinal absorption associated with an active transport system; however, caffeine (Blanchard et al 1984), allopurinol (Patel & Kramer 1986) and uric acid (Dukes et al 1982) are absorbed by passive diffusion.

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The pharmacokinetics of the neonate are known to differ from that of the adult, and the differences in metabolism, kidney excretion and extracellular volume have been studied. However, despite reports of differences in the gastrointestinal absorption rate of some drugs between the neonatal and adult period (Morselli 1976; Smith & Fisher 1980), little work has been done on examining how the permeability of drugs through the gastrointestinal membrane varies with age. During the neonatal period, the intestinal mucosa of the mammalian species remains immature. As the physiological, morphological and functional characteristics of the gastrointestinal tract change during postnatal development (Jones 1972; Paul et al 1977; Pang et al 1983), the gastrointestinal absorption of drugs should also differ with age. In our previous studies the gastrointestinal absorption of poorly absorbed sulfaguanidine (Mizuno et al 1987) and β-lactam antibiotics (Morita et al 1990) in neonatal rat (1-week-old) was greater than that in adult rat. However, it is not clear whether or not the permeability of drugs through the gastrointestinal membrane varies with age. Although acyclovir is widely used for treating infant herpes simplex infections (Blum et al 1982; Sullender et al 1987), little is known about the relationship between the gastrointestinal absorption of acyclovir and age. The present study was designed to examine the age dependency of the intestinal absorption of acyclovir and its membrane transport mechanism in rats. The rat was chosen as the animal model since the fraction absorbed orally in rats is similar to that in man (de Miranda et al 1982a).

Materials and Methods

Materials

Acyclovir was donated by Nippon Wellcome Co. Ltd. Sodium azide, ouabain, 2,4-dinitrophenol, 2-deoxyguanosine, guanine, adenine and uridine were obtained from Nakarai Chemicals Ltd (Kyoto, Japan). All other chemicals used were of analytical reagent grade.

Animals

Wistar rats, aged 1 week (males and females, 8–11 g), 2·5 weeks (males and females, 19–26 g), 3 weeks (males and females, 38–52 g) and 8 weeks (males, 210–238 g) were fasted overnight before and during the study. Rats were kept at 37°C using thermostatically controlled plates during the experiments.

Animal experiment

In-vivo. a) Intravenous administration: Rats were anaesthetized with ether. Part of the cervicalis of each rat was opened and 20 mg kg^{-1} of acyclovir sodium in solution (20 mg mL^{-1}) was injected into the jugular vein using a microsyringe. *b) Oral administration:* Rats were given 20 mg kg^{-1} of acyclovir sodium in solution (2 mg mL^{-1}) into the stomach via a polyethylene tube (i.d. 0·28 mm, o.d. 0·61 mm). In the dose-ranging experiment, the doses were as follows: 5, 10, 25 and 50 mg kg^{-1} for 2·5-week-old rats, and 5, 20, 50 and 100 mg kg^{-1} for 8-week-old rats. Blood samples (0·15 mL) were collected from the jugular vein at regular intervals after drug administration under light ether anaesthesia, and centrifuged immediately after collection to give plasma which was preserved at −40°C until analysis.

In-vitro experiment (everted sac method). Rats were anaesthetized with pentobarbitone (30 mg kg^{-1}) by subcutaneous injection and a midline abdominal incision was made. The rats were killed by cardiac puncture. The small intestine from the ligament of Treitz to the ileocaecal junction was rapidly removed and everted with a glass rod. The length of intestine and volume at the serosal and mucosal sides at different weeks of age were as follows:

Age (weeks)	Length (cm)	Number of sacs used	Volume at serosal side (mL)	Volume at mucosal side (mL)
8	7	1	0·7	60
4	6	1	0·33	30
2·5, 3	4	2	0·24	10

The everted sac was filled with Krebs-Henseleit bicarbonate buffer (pH 7·4) containing 0·4% glucose and pre-gassed with 95% O_2–5% CO_2. The sac was incubated at 37°C in a glass vessel containing the same buffer solution and gassed with 95% O_2–5% CO_2. After 5 min, the drug solution (5 μM–1 mM) was added to the glass vessel and the vessel was further incubated. The concentrations of acyclovir in the serosal side and the mucosal side were determined by HPLC.

HPLC assay for acyclovir

The concentration of acyclovir in plasma, mucosal and serosal solution was determined by HPLC (Salamoun et al 1987). To 0·05 mL of sample solution, 0·05 mL of distilled water and 0·5 mL of acetonitrile were added with vigorous mixing for 1 min. The mixture was centrifuged at 3000 rev min^{-1} for 10 min. The supernatant (0·05 mL) was evaporated to dryness below 30°C. The dry residue was dissolved in 1 mL of mobile phase and shaken for 30 s; 100 μL of the solution was applied to a Hitachi Model L-6000 HPLC chromatograph equipped with a fluorescence detector (F-1100, ex; 270 nm: em; 370 nm, sensitivity 1 aufs). The stainless-steel column, 15 cm × 4·6 mm i.d., was packed with Chemcosorb 5-ODS-H (5 μm particles) (Chemco Co., Tokyo, Japan). The mobile phase was methanol-phosphate buffer (89 mL of 0·2 M NaOH, 250 mL of 0·2 M KH_2PO_4 and 661 mL of H_2O pH 6·6) in a 20:80 ratio. Sulphuric acid (0·35 M) was introduced for post-column acidification to enhance the fluorescence intensity. The flow rates of the mobile phase and the fluorescent phase were 0·7 and 0·6 mL min^{-1}, respectively.

Data analysis

Plasma concentration-time curves were analysed according to the least squares regression analysis program MULTI (Yamaoka et al 1981). AUC values and the mean residence time (MRT) were calculated by standard linear trapezoidal integration with extrapolation to infinite time. The steady-state distribution volume (Vd_{ss}) and the total body clearance (CL_t) were estimated as described by Yamaoka et al (1983). The absolute bioavailability was expressed as:

$$\text{Bioavailability} = AUC_{0-\infty}\ \text{(p.o.)}/AUC_{0-\infty}\ \text{(i.v.)}$$

The mean absorption time (MAT) was calculated as follows:

$$MAT = MRT\ \text{(p.o.)} - MRT\ \text{(i.v.)}$$

The significant difference in pharmacokinetic parameters of acyclovir was assessed by means of Student's *t*-test.

Results and Discussion

Fig. 1 represents the mean plasma concentration vs time profile of acyclovir after intravenous administration of 20 mg kg^{-1} to rats of different ages (1, 2·5, 3 and 8 weeks).

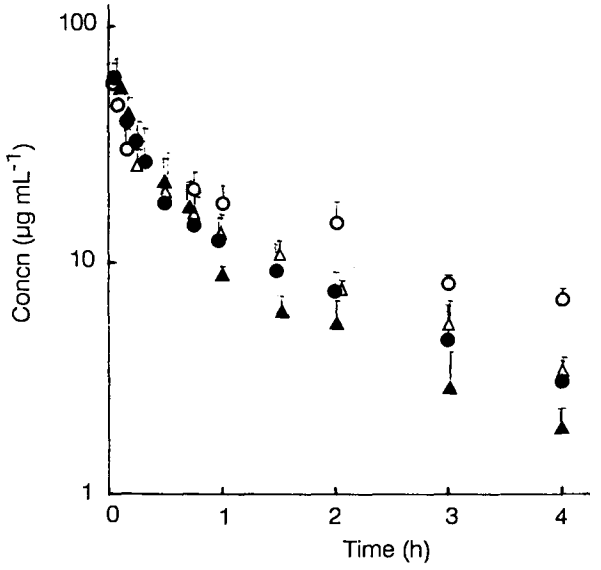

FIG. 1. Plasma concentration of acyclovir after intravenous administration (20 mg kg^{-1}) to 1- (○), 2·5- (●), 3- (▲) and 8-week-old rats (△). Each point represents the mean ± s.d. of 3 to 5 rats.

Table 1. Pharmacokinetic parameters after intravenous administration of acyclovir (20 mg kg^{-1}) to 1-, 2·5-, 3- and 8-week-old rats.

	Age (weeks)			
Parameter	1	2·5	3	8
C_1 ($\mu g\ mL^{-1}$)	51·59 ± 7·74	54·86 ± 2·42	47·79 ± 9·02	66·36 ± 10·52
C_2 ($\mu g\ mL^{-1}$)	24·77 ± 4·71	18·62 ± 4·74	28·18 ± 11·60	22·05 ± 5·01
λ_1 (h^{-1})	11·57 ± 3·82	5·19 ± 0·50[a]	7·37 ± 2·42	9·37 ± 0·85
λ_2 (h^{-1})	0·26 ± 0·04[a, b]	0·45 ± 0·11	0·85 ± 0·29	0·50 ± 0·13
Vc ($L\ kg^{-1}$)	0·27 ± 0·04	0·27 ± 0·03	0·26 ± 0·02	0·23 ± 0·03
K_{12} (h^{-1})	8·87 ± 3·47[b]	2·56 ± 0·20[a]	2·93 ± 0·98	5·45 ± 0·85
K_{21} (h^{-1})	4·69 ± 1·66	1·66 ± 0·40[a]	3·30 ± 1·55	2·70 ± 0·45
K_{10} (h^{-1})	0·79 ± 0·21[a, b]	1·43 ± 0·24	1·99 ± 0·60	1·72 ± 0·32
$AUC_{0-\infty}$ ($\mu g\ h\ mL^{-1}$)	102·82 ± 27·08[a, b]	52·22 ± 7·40	40·98 ± 14·27	50·51 ± 6·24
MRT (h)	3·55 ± 0·45[a, b]	2·01 ± 0·26[b]	1·00 ± 0·17[a]	1·80 ± 0·36
Vd_{ss} ($L\ kg^{-1}$)	0·76 ± 0·12	0·72 ± 0·17	0·53 ± 0·14	0·70 ± 0·15
CL ($L\ h^{-1}\ kg^{-1}$)	0·21 ± 0·06[a]	0·39 ± 0·06	0·53 ± 0·15	0·40 ± 0·01

Data are mean ± s.d. of 3 to 5 rats. [a] $P < 0·05$ compared with 8-week-old rats. [b] $P < 0·05$ compared with 3-week-old rats.

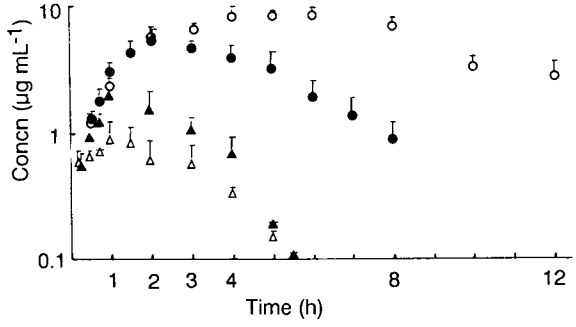

FIG. 2. Plasma concentration of acyclovir after oral administration (20 mg kg^{-1}) to 1- (○), 2·5- (●), 3- (▲) and 8-week-old rats (△). Each point represents the mean ± s.d. of 3 to 5 rats.

The pharmacokinetic parameters are shown in Table 1. The data fitted the two-compartment model expressed by the formula for rats of all ages, $C_p = C_1^{-\lambda 1t} + C_2^{-\lambda 2t}$, where C_p is the drug concentration in the plasma at time t. The constants C_1 and C_2 are intercepts on the y-axis for each exponential segment of the curve in the equation. The decrease of acyclovir from the plasma in 1-week-old rats was the slowest. Acyclovir is eliminated from the body primarily by renal excretion (Blum et al 1982). In 1-week-old rats, renal elimination is low because of glomerular and tubular immaturity.

Fig. 2 represents the mean plasma concentration vs time profile of acyclovir after oral administration of 20 mg kg^{-1} to rats of different ages (1, 2·5, 3 and 8 weeks). The pharmacokinetic parameters calculated for these are shown in Table 2. The values of MAT in 1- and 2·5-week-old rats were lower than those in 3- and 8-week-old rats. This result has indicated that the gastrointestinal absorption continued over an extended time because of weak peristaltic movement and delayed gastric emptying (Morselli et al 1980). Elimination of acyclovir from the plasma in 1- and 2·5-week-old rats tended to be slower than that in 3- and 8-week-old rats. The absolute bioavailabilities for 1-, 2·5-, 3- and 8-week-old rats were 77·59, 51·52, 14·61 and 7·30%, respectively. The intestinal mucosal membrane in 1- and 2·5-week-old rats differs biochemically from that in adults, and their intestinal mucous membrane barrier is incomplete. The difference in gastrointestinal absorption rate between 2·5- and 3-week-old rats was particularly marked and this period coincides with weaning, during which food content changes and morphological and chemical growth is promoted (Westrom et al 1984; Muto 1988).

We studied the influence of the dose-dependency on the absorption in 2·5- and 8-week-old rats. Fig. 3 shows the relationship between dose and $AUC_{0-\infty}$ after oral administration to 2·5- and 8-week-old rats. In the ranges of 5–25 and 5–50 mg kg^{-1} in 2·5- and 8-week-old rats, respectively, there was a linear relationship between doses and AUC values but at higher doses, the gastrointestinal absorption became saturated for both age groups. De Miranda et al (1981) have reported such dose dependency for rat and mouse; at high doses beyond the solubility limit, the absorption rate decreased in the range of 100–900 mg kg^{-1} for suspensions. De Miranda et al (1982a) have also demonstrated such dose dependency for dog; the best gastrointestinal absorption was recorded for this species, but the absorption rate decreased in the range 5–50 mg kg^{-1} for the drug given in capsule form. Therefore, it cannot be stated with certainty that the dose-dependency depends on the solubility or other factors. Nine

Table 2. Pharmacokinetic parameters after oral administration of acyclovir (20 mg kg^{-1}) to 1-, 2·5-, 3- and 8-week-old rats.

	Age (weeks)			
Parameter	1	2·5	3	8
MAT (h)	3·65 ± 0·38[a, b]	2·23 ± 0·25[a, b]	1·41 ± 0·19	1·45 ± 0·39
$AUC_{0-\infty}$ ($\mu g\ h\ mL^{-1}$)	76·99 ± 11·31[a, b]	27·28 ± 6·68[a, b]	6·24 ± 2·04[a]	3·48 ± 0·37
Bioavailability (%)	77·59 ± 0·38[a, b]	51·52 ± 7·17[a, b]	14·61 ± 4·76[a]	7·30 ± 0·72

Data are mean ± s.d. of 3 to 5 rats. [a] $P < 0·05$ compared with 8-week-old rats. [b] $P < 0·05$ compared with 3-week-old rats.

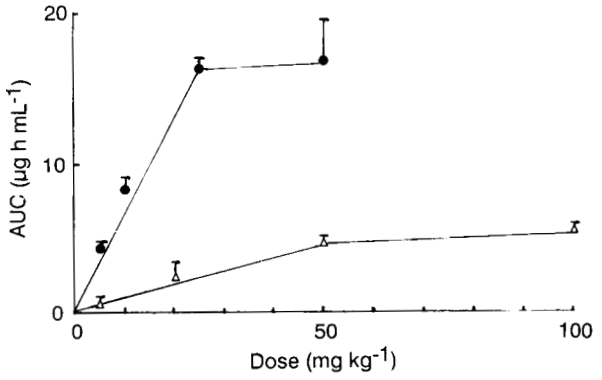

FIG. 3. Relationship between dose and $AUC_{0-\infty}$ after oral administration to 2·5- (●) and 8-week-old rats (△). Each point represents the mean ± s.d. of 3 experiments.

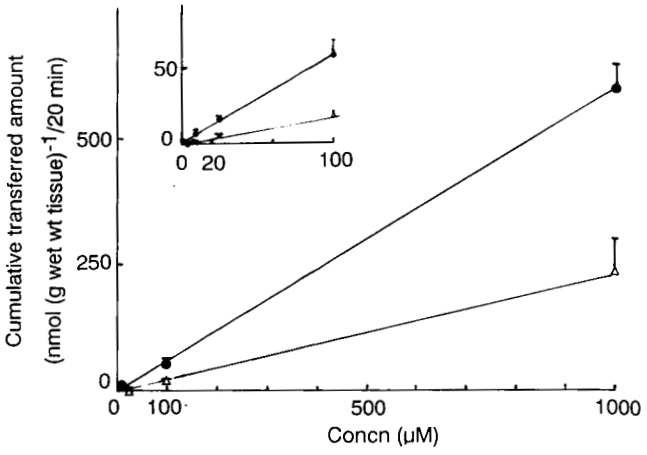

FIG. 4. Effect of initial mucosal concentration of acyclovir on the cumulative amount transferred from the mucosal to the serosal side in 20 min in 2·5- (●), and 8-week-old rats (△). Each point represents the mean ± s.d. of 3 rats.

Table 3. Transferred amount of acyclovir from the mucosal to the serosal side in rats of different ages.

Age (weeks)	Transferred amount nmol (g wet tissue)$^{-1}$ min^{-1}
2·5	0·285 ± 0·049[a]
3	0·161 ± 0·057
4	0·175 ± 0·048
8	0·177 ± 0·059

Data are mean ± s.d. of 5 rats. Initial concentration of acyclovir at the mucosal side was 10 μM. [a] $P < 0·01$ compared with 8-week-old rats.

percent of acyclovir is metabolized in the body (de Miranda et al 1982b) and as the elimination from the kidney does not show saturation in the range of experimental concentrations, the dose-dependency may be attributable to saturation in the process of absorption, or precipitation in the gastrointestinal tract because of the poor solubility of acyclovir.

The intestinal transport mechanism was further studied using the everted sac method. Table 3 gives the amounts of acyclovir transferred from the mucosal side to the serosal side in rats of different ages. The amount transferred in 2·5-week-old rats was significantly higher than that from sacs from 3-, 4- and 8-week-old rats. These in-vitro results showed

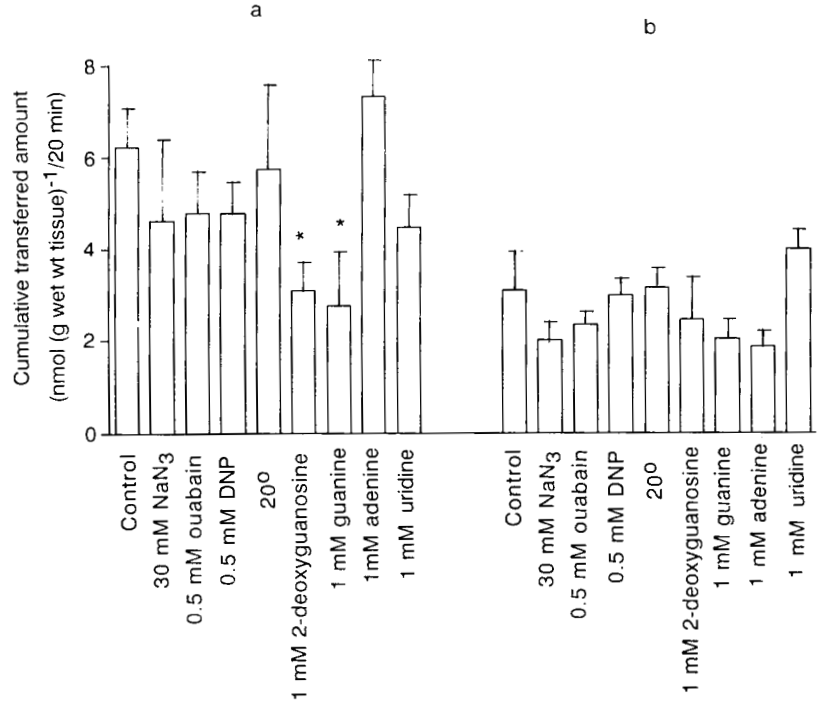

FIG. 5. Effect of metabolic inhibitors and purine and pyrimidine analogues on the cumulative amount of acyclovir transferred from the mucosal to the serosal side in 20 min in (a) 2·5-week-old rats and (b) 8-week-old rats. Each column represents the mean ± s.d. of 3 rats. Initial concentration of acyclovir on the mucosal side is 10 μM. * $P < 0·05$ compared with control.

the same tendency as the in-vivo results, with the permeability changing during the weaning period.

Fig. 4 shows the relationship between the transferred amount and the concentration of acyclovir at the mucosal side. Transferred amounts in 2·5- and 8-week-old rats were linear over the range 5 μM to 5 mM; no saturation phenomenon of absorption was detected.

The influence of metabolic inhibitors (sodium azide, 2,4-dinitrophenol, ouabain), pyrimidine and purine analogues (2-deoxyguanosine, guanine, adenine, uridine) on the permeation of acyclovir was also studied (Fig. 5a, b). As sodium azide and 2,4-dinitrophenol did not affect the permeation of acyclovir at either age examined, the transport seems to be energy-independent. As oubain did not inhibit the permeation, there seems to be no participation by Na-K-ATPase. However, 2-deoxyguanosine and guanine inhibited the permeation in the 2·5-week-old rat and adenine showed a tendency to inhibit the permeation in the 2·5-week-old rat but to increase it in the 8-week-old rat. Uridine which has been reported to display Na-K-dependent uptake (Schwenk et al 1984), did not influence the permeation. These results suggest a difference in the membrane permeability between 2·5- and 8-week-old rats, but we found no evidence of an uphill transport system.

The mechanism of the gastrointestinal absorption of acyclovir is predominantly via passive diffusion with little or no participation of active transport at either age. The dose-dependency after oral administration (Fig. 3) is probably not due to the saturation phenomenon in the absorption process, but rather to precipitation of acyclovir in the gastrointestinal tract due to a drop in the pH from 9·5, at which it is relatively soluble, to pH 7, at which its solubility is one quarter. Therefore, we suggest that the change of absorption in the growing period, is affected little or only very slightly by a special transport system. The uptake mechanism of acyclovir in adult rat has been reported to be predominantly via passive diffusion (Meadows & Dressman 1990) and our data support this. Further study is needed on the gastrointestinal absorption route (transcellular, paracellular) and factors which change the gastrointestinal absorption during weaning.

Acknowledgement

We thank Ms Y. Nakanishi and Ms K. Matsumoto for their help during this study.

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