Human gastrointestinal absorption of acyclovir from tablet duodenal infusion and sipped solution

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On two occasions at least 1 week apart, nine healthy male volunteers were administered in random order either 2×200 mg (1.8 mmol) acyclovir tablets or 400 mg of acyclovir in 500 ml of 5% dextrose solution which was infused at constant rate into the duodenum over 4 h. Six of the subjects subsequently sipped the same solution at the rate of 10.4 ml in each 5 min period for 4 h. Blood and urine were sampled over 24 h for each mode of administration. Acyclovir was assayed by radioimmunoassay. Mean areas under the plasma concentration–time curves (AUCs) $\pm$ s.d. for tablet (T), intraduodenal infusion (I) and sipping (S) were, respectively: $T = 14.7 \pm 5.1$; $I = 24.6 \pm 5.1$; $S = 28.4 \pm 9.5$ ($n = 6$) $\mu\text{mol l}^{-1} \text{ h}$. AUCs for I and S were significantly greater than that for T ($2P < 0.05$). Mean apparent maximum plasma concentrations (C_{max}) $\pm$ s.d. were $T = 3.8 \pm 1.5$; $I = 4.8 \pm 0.9$; $S = 5.1 \pm 1.5$ $\mu\text{mol l}^{-1}$. This trend to higher values for I and S was not significant. Mean apparent plasma disappearance half-lives ($t_{1/2}$) $\pm$ s.d. were respectively $T = 2.3 \pm 0.4$; $I = 2.7 \pm 0.5$; $S = 3.0 \pm 0.2$ h, I being significantly greater than T ($2P < 0.05$), as was S greater than T ($2P < 0.01$). The mean 24 h urinary recovery $\pm$ s.d. of acyclovir ($n = 8$) was $T = 309 \pm 119$ μmol (17% of dose); $I = 471 \pm 83$ μmol (26% of dose); $S = 507 \pm 180$ μmol (28% of dose). $I > T$ ($P < 0.01$), $S > T$ ($P < 0.05$). Acyclovir absorption is increased when contact time of a solution with the absorptive area of the human gut is increased as compared with absorption available from the tablet. This suggests capacity limited absorption.

Keywords acyclovir capacity limitation gastrointestinal absorption

Introduction

Acyclovir 9-(2-hydroxyethoxy methyl) guanine is an agent active *in vitro* against many of the Herpes viruses (Schaeffer *et al.*, 1978). With the exception of some urinary obstruction if renal tubular concentration is allowed to rise too high it is virtually non-toxic to man and should provide an effective chemotherapy. However it is not very soluble so absorption is incomplete and peak plasma concentrations are shortlived after oral dosing which is repeated frequently in the empirically derived scheme now extensively

used in treating Herpes simplex (Rogers & Fowle, 1983). From the relation between achievable plasma concentrations and lethal concentrations *in vitro* efficacy in treating other herpes virus infections ought to be possible. One problem is the suggestion of capacity limited absorption described in early reports (De Miranda & Blum, 1983) where the uptake after oral administration does not increase proportionately with increases in dose. A possible pharmaceutical way to overcome this problem would be a sustained release

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preparation which might reduce the frequency of dosing by reducing the differences in concentrations of acyclovir between the upper and lower reaches of the intestine. In order to provide an estimate of how much could be expected if such a presentation could be prepared we performed the following experiment.

In principle this was to infuse into the duodenum over the empirically derived dosage interval, namely 4 h, 400 mg acyclovir in solution. We compared the resultant concentration profile with that observed over the same interval after taking the commonly prescribed tablet form. The stomach was bypassed to avoid the possibility of dissolution and thereafter precipitation in an uncontrolled manner because the solubility of acyclovir goes through a minimum at around pH 7.0.

Methods

Study design

All subjects fasted from midnight before each laboratory attendance and abstained from alcohol for 24 h. One of two treatments was randomly assigned to each of them on the first occasion and the alternative was taken 1 week later. The treatments were: (a) Ingest 2×200 mg acyclovir tablets, with 200 ml of 5% dextrose solution and drink another 100 ml at exactly 1 h, 2 h and 3 h later. (b) A standard nasoduodenal tube of 10 ml capacity was positioned (by Dr P. Isaacs) under X-ray fluoroscopy. Acyclovir (400 mg) in 500 ml 5% dextrose solution was infused down it at a constant rate of 2.08 ml min^{-1} over 4 h. Then the tube was flushed with 10 ml 5% dextrose. Immediately after this the tip was confirmed to be still in the duodenum by fluoroscopy.

A 25 ml aliquot of urine was retained when the bladder was emptied immediately before each acyclovir administration. Volunteers sat in a semi-erect position (except during micturition) for the first 4 h of the study so as to reduce variation in gastric emptying. Venous blood was sampled via an indwelling cannula in the forearm at times 0 and every 15 min for 2.5 h and then hourly from 3–10 h and then at 12, 14, 16 and 24 h. Blood was expeditiously centrifuged (maximum time 20 min) and plasma stored at -20°C to await assay. Aliquots (25 ml) of urine were likewise stored from that passed in consecutive 2 h intervals between 0 and 12 h, and in the single interval from 12 to 24 h. Total urine volumes were recorded.

In view of the practical implications of the result it became of interest to see if the improved

absorption could be obtained without bypassing the stomach. Several weeks later, six of the original volunteers participated in a further clarifying study. They fasted as before but from time 0 they continuously sipped the acyclovir solution so that it had to traverse the pyloric sphincter. The sipping rate of 10.4 ml every 5 min was maintained for exactly 4 h of a fluid with a composition of 400 mg acyclovir in 500 ml 5% dextrose. All other aspects such as posture, blood and urine sampling procedures and meal times were kept unchanged. The study design was approved by Guy's Hospital Ethics Committee.

Subject selection

Nine male student volunteers judged healthy after physical examination and after normal results from routine blood biochemistry and haematology tests and a urine screen participated. Their age range was 20–29 years, the mean body surface area was 2.06 m^2 (s.d. ± 0.18). The mean Quetelet index (M/H^2 , the body mass for height index) was 24.8 (s.d. ± 3.1) (normal range 19–24.9 (Llewellyn-Jones & Abraham, 1984)). None were then on medicines but two were smokers. All gave written consent for the study.

Acyclovir assay

Acyclovir was assayed in duplicate in plasma and urine samples freshly thawed using a radioimmunoassay double antibody precipitation technique (Jeal & Bye, 1983). This uses a specific mouse monoclonal antibody to acyclovir—with donkey anti-mouse IgG antibody. The assay is specific, with a linear standard curve over the concentration range $0.02\text{--}0.5 \mu\text{mol l}^{-1}$. The coefficient of variation between assays was 5–10%.

Data analysis

Pharmacokinetics parameters were obtained using the NONLIN pharmacokinetic program (Metzler *et al.*, 1974) and preliminary estimates obtained by C. Strip (Sedman & Wagner, 1974). Comparisons between tablet and infusion for all nine subjects were made by matched pairs *t*-tests for each pharmacokinetic parameter. Observed t_{max} comparison was by Wilcoxon matched pairs signed ranks test. In addition, data from the six subjects who took part on the sipping occasion were submitted to variance analysis for assessment of treatment differences; Duncan's multiple range test was used to elucidate these differences. In all tests, significance was $2P < 0.05$.

Results

Figure 1 shows the three mean plasma concentration–time profiles for tablet, infusion and sipping, respectively. Table 1 shows the means of pharmacokinetic parameters derived from individual curves. Areas under the profiles following both duodenal infusion and sipping were almost twice that following the tablet. The differences were significant. The peak concentrations after infusion and sipping tended to be higher than that after the tablet but the difference was not

Figure 1 Mean plasma acyclovir concentrations ($\mu\text{mol l}^{-1}$) vs time (h) following administration of 400 mg of acyclovir by tablet ($\blacksquare$, $n = 9$); by duodenal infusion ($\blacktriangle$, $n = 9$); by sipped solution ($\bullet$, $n = 6$).

significant. In keeping with the evidence for greater absorption which the data suggest for duodenal infusion and sipping over tablets were the smaller coefficients of variation for C_{max} which were respectively 18.7%, 28.9% and 40%.

Table 1 also shows the mean 24 h urinary recoveries of acyclovir from infusion, sipping and tablet. They represented 26%, 28% and 17% of the dose, respectively.

Discussion

The data show that reducing the delivery rate of acyclovir to its absorption site in the gut does statistically significantly improve the amount absorbed. Whether this is worthwhile depends on whether the peak concentration only has momentarily to reach the range associated with antiviral effect or whether the mean concentration in an individual's plasma is important. Achievement of a higher peak concentration after duodenal infusion and sipping was not always obtained but the trend suggests that generally it would be. The decline from the maximum concentration is, not surprisingly, delayed after duodenal infusion and sipping because the absorption process is deliberately protracted. The apparent plasma disappearance half lives reflect this. The effect contributes to a higher mean concentration prevailing for a longer period after both the duodenal infusion and sipping than after the tablet. Thus this study shows how a controlled delivery system would have to perform to improve the pharmacokinetic factors of importance for antiviral activity while simultaneously economising on the quantity of drug ingested. In the event, such a pharmaceutical system is not likely to be required because a prodrug with excellent absorptive properties has been developed (6-deoxyacyclovir) and has been used in clinical

Table 1 Pharmacokinetic parameters and urinary recoveries of acyclovir when given as tablet ($n = 9$); duodenal infusion ($n = 9$) and sipped solution ($n = 6$). Means $\pm$ s.d.; NS = non-significant

		Tablet (T)	Infusion (I)	Sipping (S)	
AUC ($\mu\text{mol l}^{-1} \text{ h}$)	$n = 9$	14.7 ± 5.1	24.6 ± 5.1	—	$I > T; 2P < 0.01$
	$n = 6$	14.5 ± 6.3	24.4 ± 5.8	28.4 ± 9.5	$I, S > T; 2P < 0.01$
C_{max} ($\mu\text{mol l}^{-1}$)	$n = 9$	3.8 ± 1.5	4.8 ± 0.9	—	NS
	$n = 6$	3.8 ± 1.9	4.7 ± 0.8	5.1 ± 1.5	NS
t_{max} (h)	$n = 9$	1.4 ± 0.3	3.8 ± 0.7	—	$I > T; 2P < 0.01$
	$n = 6$	1.3 ± 0.3	3.6 ± 0.7	4.0 ± 0.3	NS
Apparent $t_{1/2}$ (h)	$n = 9$	2.3 ± 0.4	2.7 ± 0.5	—	$I > T; 2P < 0.05$
	$n = 6$	2.5 ± 0.3	2.7 ± 0.4	3.0 ± 0.2	$S > T; 2P < 0.01$
24 h urinary recovery (μmol)	$n = 8$	309 ± 119	471 ± 83	—	$I > T; 2P < 0.01$
	$n = 6$	—	—	507 ± 180	$S > T; 2P < 0.05$

practice (Selby *et al.*, 1984). However the study is simple and could be repeated on other drugs with capacity limited absorption to give encouragement or guidance for pharmaceutical development. The limitations could be in solubility, absorptive area ('window') or in carrier mediated transport. Although our study was not designed to distinguish between them, insolubility seems to be the likeliest cause for acyclovir.

The comparison of results from sipping and infusion cannot be strict because sipping was an

after thought and so not randomised. However, similar results should be expected as gastric emptying of liquids in the fasting state should not be hindered. The original reason for duodenal intubation was to avoid any possible dissolution or precipitation into a form with altered and uncontrolled physical chemical properties due to an acidic environment. When this potential effect is not important a sipping study, simple but boring for the subjects, may prove helpful.

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