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The influence of food on the absorption of acyclovir: a pharmacokinetic and scintigraphic assessment

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Summary

The effects of a light or heavy breakfast on the absorption of acyclovir (400 mg), containing technetium-99m labelled resin and administered as a suspension to 6 healthy volunteers, has been followed using gamma scintigraphy and measurement of plasma concentration. The heavier meal slowed the rate of gastric emptying, prolonged small intestinal transit time and significantly decreased absorption of the drug. No correlation was found between the small intestinal transit time and the area under the plasma concentration time curve.

Introduction

Acyclovir, 9-((2-hydroxyethoxy)-methyl)guanine is an established antiviral drug active against herpes simplex and varicella/zoster viruses. It is incompletely absorbed with an estimated bioavailability of approximately 20% from 200 mg single doses when administered orally as a solution or capsule (de Miranda and Blum, 1983). It has been proposed that the net absorption of acyclovir is approximately proportional to the dose in the range 200–600 mg (de Miranda and Blum, 1983); however, an earlier study by Brigden and co-workers (1980) suggested that the absorption of acyclovir is dose dependent after the administration of single doses in the range of 100 and 600 mg.

Few drugs are well absorbed by the stomach and the small intestine is the major site of absorption, hence the rate of gastric emptying is assumed to be the prime determinant of delivery of the drug to the site of absorption. Heading and co-workers (1973) have demonstrated a significant correlation between gastric emptying and the urinary excretion of orally-administered paracetamol. Lewis and co-workers (1986) have shown that reduction of the delivery rate of acyclovir to the small intestine, significantly increases the amount of drug absorbed.

A delay of gastric emptying provides a prolonged period for dissolution which would be expected to increase the availability of drugs with low water solubility (Ho et al., 1983). Acyclovir is poorly soluble in both water and octanol but solubility in acid is high. Reduction of the rate of

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gastric emptying may therefore increase the absorption of acyclovir by two mechanisms, firstly by increasing the contact time with gastric acid and secondly by slow delivery from the stomach to the sites of absorption in the intestine. This theory has been investigated by administering a suspension of acyclovir containing a non-absorbable radiolabelled marker to healthy subjects immediately following heavy and light meals, and measuring the blood levels of the drug over 24 h periods. Transit of the marker was followed by gamma scintigraphy.

Materials and Methods

Individual doses of an acyclovir suspension (400 mg in 20 ml) were supplied by The Wellcome Foundation Ltd.

Anion exchange resin [IRA 400 (Cl)] beads of 0.5–0.7 mm diameter were radiolabelled with [^{99m}Tc]pertechnetate to monitor gastric emptying and intestinal transit. It was established that the technetium remained associated with the resin in gastric juice or simulated intestinal fluid, with less than 5% loss of the marker from the preparation after 4 h incubation at 37 °C. 110 mg of the radiolabelled resin was added to 20 ml of the acyclovir suspension. At the time of administration, each 400 mg dose contained 3 MBq technetium-99m.

The light meal (1500 kJ) comprised of: two toasted slices of white bread lightly buttered and with a scrape of marmalade, and 200 ml of orange juice; and the heavy meal (3600 kJ): two sausages, a rasher of bacon, a fried egg, a fried tomato, a piece of fried bread and coffee with milk.

Six healthy male volunteers aged 20–23 years participated in the study on two occasions. All subjects gave written informed consent and the protocol was approved by the local ethical committee. After an overnight fast, 3 subjects consumed a heavy breakfast and 3 a light breakfast at 08.30 h. Within 20 min of eating, each subject drank the radiolabelled suspension of acyclovir and resin followed by a further 100 ml water. The subjects refrained from eating or drinking for 2 h after dosing, and all consumed a light lunch at 13.00 h. From 17.00 h the subjects were free to consume their own meals. One week later the cross-over study was completed.

Using a gamma camera, anterior and posterior images of the abdomen, each of 60 s duration, were recorded immediately after dosing. Repeated imaging was undertaken at intervals over the following 10 h, and the data stored by computer for subsequent analysis. As an aid to image interpretation anatomical reference markers were taped to the skin anteriorly and posteriorly over the right lobe of the liver. Dispersion of the radiolabelled resin facilitated identification of the position of the stomach and colon relative to the reference markers. Regions of interest were created over the stomach and colon and the total counts in each area determined. In order to correct for a combination of tissue absorption and distance attenuation of the radiation energy, the geometric means from each pair of anterior and posterior views were calculated. Data was corrected for background contribution and radioactive decay and the results expressed as a proportion of the original activity.

Venous blood samples were collected into heparinised tubes at intervals over a period of 24 h; the first sample being taken prior to the administration of the acyclovir. The tubes were centrifuged, the plasma removed and stored at −20 °C.

TABLE 1

Gastric T_{50} and small intestinal transit times following light and heavy meals

Subject	Gastric T_{50} (min)		Small intestinal transit time (min)	
	Light meal	Heavy meal	Light meal	Heavy meal
PW	42	137	133	263
SR	47	82	160	236
NR	25	45	175	407
NA	57	85	220	282
NG	70	132	245	348
TJ	42	165	146	123
Mean ±S.D.	47 ± 15	108 ± 44	180 ± 44	277 ± 218
Wilcoxon Rank test	$P > 0.05$		$P > 0.05$	

TABLE 2

Pharmacokinetic parameters for acyclovir 400 mg suspension administered after light and heavy meals (mean ± S.D.)

	Light	Heavy
Lag time (h)	0.09 ± 0.10	0.09 ± 0.09
AUC_{0-24h} (μmol/l/h)	19.33 ± 1.58	15.87 ± 1.77 **
Absorption half-life (h)	0.40 ± 0.11	0.57 ± 0.16
Terminal elimination half-life (h)	4.23 ± 1.7	5.55 ± 0.92
C_{max} (μmol/l)	4.11 ± 0.68	2.46 ± 0.35 **
T_{max} (h)	1.67 ± 0.26	1.83 ± 0.68

** $P < 0.05$ paired t-test.

Acyclovir levels in the samples were measured using the modification of Jeal and coworkers (1982) to the radioimmunoassay described by Quinn et al. (1979).

Results

The times for half the radiolabelled resin to empty from the stomach (T_{50}) of each subject after light and heavy meals and the corresponding small intestinal transit times are given in Table 1. The small intestinal transit time (S.I.T.T.) was calculated as the time difference between the gastric emptying T_{50} and the colon arrival T_{50}. The data from the S.I.T.T. was not normally distributed and comparisons between the transit times

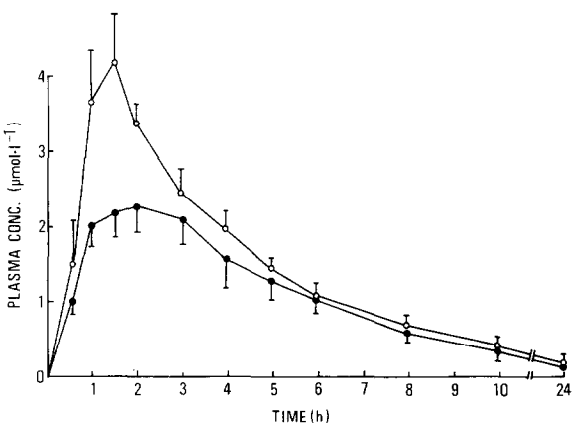

Fig. 1. Mean plasma concentrations in 6 healthy male volunteers after administration of 400 mg acyclovir with light (○) and heavy (●) breakfasts.

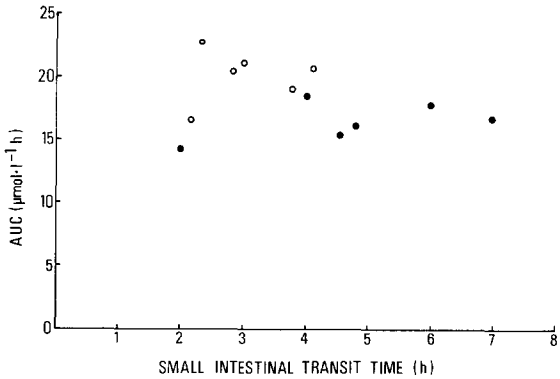

Fig. 2. Lack of a relationship between the area under the plasma concentration time curve (AUC) versus the intestinal transit time. Key: ○, light breakfast; and ●, heavy breakfast.

for light and heavy meals were carried out using a Wilcoxon signed rank test to allow for the unequal group variances. All other data were compared using a paired t-test. For all the subjects the half-times for gastric emptying were significantly greater following the heavy meal ($P < 0.05$). In general, transit through the small intestine was slower following the heavier meal, which was an unexpected finding.

Pharmacokinetic analysis was carried out assuming a two-compartment open model as described by de Miranda and co-workers (1979) using the NONLIN pharmacokinetic programme. Derived parameters are summarised in Table 2. Mean peak plasma concentrations and the area under the curve were significantly greater ($P < 0.05$, paired t-test) when the drug was given with a light meal compared to a heavy meal (Fig. 1). The calculated elimination half-life of around 6 h is approximately twice as long as that derived by other workers for similar doses. This suggests that absorption occurred over a prolonged period and may be attributed to the combination of dosage form used and the presence of food. The area under the plasma concentration time curve appears to have no correlation with the small intestinal transit time (Fig. 2).

Discussion

Previous studies have shown that within individuals, liquids, particulates (e.g. resin beads) and

single units pass through the small intestine at the same rates (Davis et al., 1986). Hence separation of the marker and suspension is unlikely and the transit time for the resin is expected to be similar to the acyclovir suspension.

Studies conducted in our laboratory have shown that S.I.T.T. was relatively unaffected by the calorific content of the meal (Davis et al., 1984), a finding which has been frequently verified in other investigations conducted by our group. However, in the present study, it appears the S.I.T.T. was increased following the heavy meal. The finding, although unexpected, was extremely useful since it allowed the examination of the effect of small intestinal transit time on acyclovir absorption. Using the method of gamma scintigraphy, small intestinal transit times have been calculated to be between 3 and 5 h in agreement with the results obtained in the present study. Although the bioavailability was reduced following coadministration of the drug with a heavy meal, there was no relationship between the area under the curve and the small intestinal transit time (Fig. 2). The time to peak plasma concentration was not significantly different with the two meals and occurred within 2 h of dosing suggesting that the site of maximum absorption is situated in the proximal small intestine. The prolonged half-life indicates that some absorption occurs throughout the gastrointestinal tract.

It has been well established that food may alter drug absorption by a variety of mechanisms including physicochemical processes such as adsorption, complexation and by interactions with physiological processes especially by gastric emptying. Toothaker and Welling (1980) have reviewed the effect of food on drug bioavailability, quoting examples which showed that absorption may be decreased, delayed or increased in the presence of food. From our own observations using pH radiotelemetry, the pH profile in the stomach following the ingestion of food is dependent on both the volume and the composition of the meal. The volume of the heavier breakfast was approximately 60% greater than the lighter meal, which would lead to increased dilution of the suspension. In addition, it would elevate gastric pH for longer than the lighter meal. Acyclovir is most soluble above pH 10 and below pH 2.2. In the conditions likely to be met in the small intestine, the maximum solubility would be estimated to be between 1 and 2 mg/ml. At pH 1.0, the solubility rises to 12 mg/ml; thus in the acidic environment of the stomach, the solubility of acyclovir will be increased and the drug will empty with the acidic chyme into the duodenum. When the acidic chyme is neutralised, the solubility of the drug will decrease and absorption would be slowed. In both cases, it would be expected that the absorption peak would be seen soon after gastric emptying had been initiated. The heavier breakfast provides a less acidic medium of greater volume, which may decrease the concentration of drug in contact with the absorbing mucosa. Lewis and co-workers (1986) have shown that acyclovir absorption is increased when contact time of the drug was prolonged by the subject sipping a solution over a 4 h period. However, the possibility cannot be ruled out that the acyclovir may be absorbed by an active transport system such as exists for purine bases in the gastrointestinal tract.

The present findings highlight an important food–drug interaction which occurs high in the gastrointestinal tract. Much has been made of the concept of intestinal reserve length (Ho et al., 1983) but the present data suggest that such a simplistic approach may be inadequate to predict the behaviour of drugs which show a marked decrease in solubility when transferred from an acidic to a more neutral medium.

References

Brigden, D., Fowle, A. and Rosling, A., Acyclovir, a new anti-herpetic drug: early experience in man with systemically administered drug. In Collier, L.H. and Oxford, J. (Eds.), *Developments in Anti-Viral Therapy*, Academic, London, 1980, pp. 53–62.

Davis, S.S., Hardy, J.G., Taylor, M.J., Whalley, D.R. and Wilson, C.G., The effect of food on the gastrointestinal transit of pellets and an osmotic device (Osmet.). *Int. J. Pharm.*, 21 (1984) 331–340.

Davis, S.S., Hardy, J.G. and Fara, J.W., Transit of pharmaceutical dosage forms through the small intestine. *Gut*, 27 (1986) 886–892.

De Miranda, P., Whitley, R.J., Blum, M.R. and seven other authors, Acyclovir kinetics after intravenous infusion. *Clin. Pharmacol. Ther.*, 26 (1979) 718–728.

De Miranda, P. and Blum, M.R., Pharmacokinetics of acyclovir after intravenous and oral administration. *J. Antimicrobiol. Chemother.*, 12 Suppl. (1983) 29–37.

Heading, R.C., Nimmo, J., Prescott, L.F. and Tothill, P., The dependence of paracetamol absorption on the rate of gastric emptying. *Br. J. Pharmacol.*, 47 (1973) 415–421.

Ho, N.F.H., Merkle, H.P. and Higuchi, W.I., Quantitative, mechanistic and physiologically realistic approach to the biopharmaceutical design of oral drug delivery systems. *Drug Dev. Ind. Pharm.*, 9 (1983) 1111–1184.

Jeal, S., Burke, C. and Bye, A., An improved radioimmunoassay for acyclovir using a monoclonal antibody. *Proc. 2nd Int. Acyclovir Symp.*, London, 1982, P–6.

Lewis, L.D., Fowle, A.S.E., Bittiner, S.B., Bye, A. and Isaacs, P.E.T., Human gastrointestinal absorption of acyclovir from tablet, duodenal infusion and sipped solution. *Br. J. Clin. Pharmacol.*, 21 (1986) 459–462.

Quinn, R.P., De Miranda, P., Gerald, H. and Good, S.S., A sensitive radioimmunoassay for the antiviral agent BW 248U{{9-(2-hydroxyethoxy)methyl}guanine}. *Anal. Biochem.*, 98 (1979) 319–328.

Toothaker, R.D. and Welling, P.G., The effect of food on drug bioavailability. *Annu. Rev. Pharmacol. Toxicol.*, 20 (1980) 173–199.