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The effect of increasing gastric pH upon the bioavailability of orally-administered foscarnet

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Abstract

For systemic use, the anti-cytomegalovirus (CMV) agent foscarnet must be given intravenously because oral administration results in unmeasurable or barely measurable plasma levels. At low pH, foscarnet decomposes via an acid-catalyzed decarboxylation; therefore, poor oral bioavailability might be due to decomposition of foscarnet in gastric acid. We evaluated whether increasing gastric pH with ranitidine would enhance the absorption of oral foscarnet in six asymptomatic HIV-infected individuals. Each volunteer received two oral 4000-mg (60 mg/kg) doses of foscarnet, preceded intravenously by a 20-min infusion of either ranitidine 50 mg in D_5W or D_5W alone in a randomized, double-blind, cross-over study. Intragastric pH monitoring revealed that subjects had evidence of gastric acid production ($pH < 2.0$) prior to administration of ranitidine and increased gastric pH ($pH > 6.0$) following ranitidine administration. Most foscarnet plasma levels were below the assay limit of detection (33 μM) with only 4/30 levels detectable after D_5W and 8/30 after ranitidine. Urinary recovery of foscarnet increased after ranitidine pretreatment. A mean recovery of 9.9% of the drug was realized in the urine in 24 h following ranitidine pretreatment compared to 6.2% of the dose after D_5W pretreatment ($P < 0.03$). We estimate that 9.9% recovery in the urine in 24 h is equivalent to absorption of 17.1% of the oral dose. In spite of the enhanced bioavailability associated with ranitidine pretreatment, the degree of absorption is still insufficient to achieve effective plasma concentrations for the treatment of CMV or acyclovir-resistant herpes viruses. We conclude that gastric acidity is a determinant of foscarnet absorption, albeit not a major one. Oral foscarnet is unlikely to be clinically useful even if administered in the setting of increased gastric pH.

Keywords: Foscarnet; Bioavailability; Antiviral; H2-blocker; Ranitidine

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Foscarnet has demonstrated clinical usefulness in the treatment of disease due to a variety of viruses including cytomegalovirus (CMV), herpes simplex virus 1 and 2 (HSV-1 and HSV-2), varicella zoster virus (VZV), most ganciclovir-resistant CMV, and most acyclovir-resistant HSV and VZV (Wagstaff and Bryson, 1994). At the current time, for systemic treatment, foscarnet must be given intravenously because oral administration has resulted in immeasurable plasma levels and poor recovery in urine, suggesting poor oral bioavailability (Sjovall et al., 1988). Oral dosing of foscarnet would be desirable, especially in the setting of a disease such as CMV retinitis where prolonged therapy is indicated.

A pyrophosphate analogue, foscarnet is the trisodium salt of phosphonoformic acid and contains three acidic hydrogens. At very low pH's, when its carboxyl group (pK_a 0.49) is in the undissociated form, foscarnet decomposes rapidly via an acid-catalyzed decarboxylation (Warren and Williams, 1971). Therefore, the poor oral bioavailability of foscarnet might be due to its decomposition in gastric acid, thus preventing absorption of intact drug. If this were true, then increasing the gastric pH would be expected to enhance foscarnet bioavailability.

Following a 20-min infusion of a single 50-mg intravenous dose of ranitidine to healthy volunteers, titratable hydrogen ion concentration is reduced to less than 30% of baseline for 2.4–3.2 h after dosing (Frank et al., 1986). The intragastric pH following administration of intravenous ranitidine rises above 3.5 within 30 min of drug dosing and remains greater than 3.5 for 3–4 h. At a pH of 3.5, less than 0.1% of foscarnet is in the undissociated form susceptible to decomposition. Based on intravenous ranitidine's ability to rapidly reduce intragastric acidity, we hypothesized that administration of ranitidine prior to the ingestion of foscarnet might improve the latter's bioavailability by raising the gastric pH, resulting in less acid-catalyzed decomposition of foscarnet.

We conducted a randomized, double-blind, cross-over, placebo-controlled bioavailability study in six asymptomatic HIV-infected individuals to determine the effect of increasing gastric pH on the oral bioavailability of foscarnet. The study was approved by our local Institutional Review Board, and written consent was obtained from each participant.

We selected a sample size of six to detect a minimum important difference in absorption of 33% with an alpha error of 0.05 and a beta error of 0.20. Since each subject served as his own control, inter-individual variability in foscarnet absorption and pharmacokinetics was not an issue.

Each subject received 4000 mg (60 mg/kg) of foscarnet orally as a 1.2% solution in D_5W on two separate occasions. Each dose was separated by 72 h. Subjects received either 50 mg intravenous ranitidine in 50 cc D_5W or 50 cc of D_5W alone in a double-blind manner, 30 min prior to foscarnet administration. The order of administration of ranitidine versus D_5W was randomized.

Using the dose of foscarnet as zero time point, intragastric pH levels were monitored by a nasogastric pH electrode at -2, -1.5, -1 h (immediately prior to the start of the intravenous infusion of ranitidine or D_5W), -0.5, 0 (just before the foscarnet dose), 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75 and 2 h. Plasma samples for determination of foscarnet concentrations were obtained at baseline and at 0.5, 1.0, 2.0, 4.0, and 6.0 h following dosing. Urine for foscarnet concentration was collected for 24 h following each dose. Foscarnet concentrations were measured in plasma and urine in batched samples using a validated HPLC method with electrochemical detection (Hassanzadeh et al., 1990). The assay has a lower limit of detection of 33 μM and a coefficient of variation of 2.4–3.3% for plasma samples and 1.7–3.5% for urine samples. Foscarnet absorption was assessed by comparing the quantity of foscarnet excreted in the urine for 24 h following each dose. After analyses were complete the order of ranitidine and placebo administration was unblinded. The ranitidine and placebo treatments were compared using a Wilcoxon signed rank test analysis for paired samples.

Due to problems with gastric probe placement, we could not measure gastric acidity during the D_5W administration in two of the six subjects;

otherwise, all subjects were found to have acidic gastric contents at baseline. Gastric pH readings increased consistently from baseline to greater than 6.0 following ranitidine administration, while D_5W caused no change from baseline gastric pH. After oral administration of the foscarnet solution, the majority of foscarnet plasma concentrations were below the limit of detection of the assay (33 μM). Only 4/30 of the foscarnet plasma concentrations were detectable in the placebo group and only 8/30 of the foscarnet plasma concentrations were detectable in the ranitidine group. The highest foscarnet plasma concentration of 80 μM was found 2 h after foscarnet administration in one subject after ranitidine pretreatment.

In all six subjects the 24-h urinary recovery of foscarnet was increased following pretreatment with ranitidine compared to placebo (Table 1). A mean of 9.9% of the administered dose of foscarnet was recovered in the urine after ranitidine pretreatment compared to a mean recovery of 6.2% of foscarnet after D_5W administration, demonstrating a modest enhancement in absorption ($P < 0.03$).

Oral administration of foscarnet was well tolerated.

Data from Noormohamed et al. (1997) indicate that 95% of an intravenous dose of foscarnet is recovered in the urine in 24 h after a single dose is administered to HIV sero-positive patients. These data suggest that virtually all absorbed foscarnet would be excreted in the urine and that the 9.9% fractional recovery in urine over 24 h is equivalent to a fractional oral absorption of 9.9%. Other data from Sjovall et al. (1989) and Aweeka et al. (1989) reveal that systemic clearance of foscarnet is approximately 2 ml/kg/min. Using this value and assuming that 9.9% of each dose of foscarnet is absorbed, we estimate that if 60 mg/kg of foscarnet were administered orally every 8 h, the resulting average steady-state foscarnet concentration would be only 21 μM. Plasma concentrations of foscarnet after intravenous doses range from 50 to 800 μM. The in vitro ED_{50} for inhibiting CMV is 100–300 μM (Oberg, 1983) and the mean ED_{50} for inhibiting 24 clinical isolates of acyclovir-resistant herpes was 75 μM (Safrin et al., 1990). Based on these data and on our findings, oral dosing of foscarnet, even in the setting of increased gastric pH, would not be expected to yield plasma concentrations in the range of the in vitro ED_{50} for inhibition of growth of CMV or acyclovir-resistant herpes. Gastric acidity does appear to be a determinant of foscarnet absorption, but increasing the gastric pH fails to provide enough of an effect on oral bioavailability to be clinically useful.

Foscarnet is known to be transported across the intestinal brush-border membrane by a sodium-phosphate cotransport carrier system (Tsuji and Tamai, 1989). Further considerations of enhancing the oral bioavailability of foscarnet may involve strategies designed to alter the activity of this transport system.

Table 1
Percent of foscarnet dose recovered in urine after 24 h

Subject	Placebo pretreatment	Ranitidine pretreatment
1	1.4	4.7
2	9.9	16.3
3	4.7	7.0
4	4.9	6.3
5	4.4	10.2
6	12.2	14.7
Mean ($\pm$S.D.)	6.2 ± 4.0*	9.9 ± 4.7*

* $P < 0.03$, Wilcoxon signed rank test, difference between groups.

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