Effect of Antacids and Ranitidine on the Single-Dose Pharmacokinetics of Fosamprenavir

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Single doses of MAALOX TC and ranitidine were administered separately with 1,400 mg of fosamprenavir (FPV). MAALOX TC decreased the area under the concentration-time curve from 0 to 24 h (AUC$_{0-24}$) for plasma amprenavir (APV) by 18% and the maximum concentration of drug in serum ($C_{\text{max}}$) by 35%; the plasma APV concentration at 12 h ($C_{12}$) increased by 14%. Ranitidine at 300 mg decreased the AUC$_{0-24}$ for plasma APV by 30% and $C_{\text{max}}$ by 51%; $C_{12}$ was unchanged. FPV may be coadministered with antacids without concern and without separation in dosing; however, caution is recommended when FPV is coadministered with histamine$_2$-receptor antagonists or proton pump inhibitors.

Fosamprenavir (FPV, GW433908) has been approved for treatment of human immunodeficiency virus (HIV)-infected adult patients. FPV, a phosphoester prodrug, is rapidly and extensively hydrolyzed to the HIV protease inhibitor amprenavir (APV) during absorption, with minimal systemic FPV exposure (12).

Due to the chemical properties of FPV, an interaction with both antacids and histamine$_2$-receptor antagonists is possible. FPV exhibits pH-dependent solubility, with maximal solubility at pH 3.3 and reduced solubility at higher pHs (5). The phosphate group on FPV could bind to the metal cations contained in antacids, which could either alter solubility or prevent pre-systemic conversion of FPV to APV. This study assessed the effects of antacids and ranitidine on single-dose plasma APV pharmacokinetics following administration of FPV.

This single-dose, open, randomized, three-way balanced crossover study included administration of 1,400 mg of FPV alone, 1,400 mg of FPV immediately following 30 ml of oral antacid (MAALOX TC; Novartis Consumer Health), 1,800 mg of magnesium hydroxide and 3,600 mg of aluminum hydroxide dried gel (2,754 mg of aluminum hydroxide), and 1,400 mg of FPV 1 h after 300 mg of ranitidine. There was a 4- to 7-day washout between each treatment. Subjects fasted overnight, continuing until 4 h after dosing. Water was permitted ad libitum during the overnight fast. The study drug was administered with 180 ml of water, and additional water was permitted ad libitum from 2 h after dosing. Blood samples were collected in sodium citrate-containing tubes (Vacutainers; Becton-Dickinson) at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, and 24 h after dosing. Prior to analysis, plasma was stored at or below 30°C, at which temperature stability has been confirmed for 32 months. Plasma APV and FPV concentrations were measured within 4 months of initial dosing using a validated high-performance liquid chromatography assay with tandem mass spectrometric detection following solid-phase extraction (the linear range for APV was 10 to 10,000 ng/ml, and that for FPV was 5 to 1,000 ng/ml).
The CI of 0.75 to 1.33 was considered clinically meaningful for APV AUC\(_0-24\) administered immediately following 30 ml of MAALOX TC, plasma \(90\%\) CI) are summarized in Table 1. When FPV was administered immediately following coadministration of FPV and ranitidine, the AUC\(_0\)–\(24\) increased gastric pH has also decreased the absorption of the HIV protease inhibitors atazanavir (2) and indinavir (3) but to a much greater magnitude (>80% decrease in plasma atazanavir and indinavir exposures) than that observed for FPV.

Both steady-state plasma protease inhibitor AUCs (AUC\(_{TT,8}\) [area under the curve over the dosing interval at steady state]) and trough concentrations (C\(_{T,8}\) [plasma concentration at the end of the dosing interval at steady state]) have been correlated with antiviral activity and development of resistance (1, 4, 6–8, 10). Plasma APV C\(_{T,8}\) was determined to be a better predictor of viral load reduction at 4 weeks than AUC\(_{TT,8}\) (9; G. L. Drusano, Abstr. 37th Intersci. Conf. Antimicrob. Agents Chemother., abstr. A-16, 1997). If it is assumed that single-dose plasma APV C\(_{12}\) is a surrogate for plasma APV C\(_{T,8}\), the lack of effect of either MAALOX or ranitidine on plasma APV C\(_{12}\) suggests that plasma APV C\(_{T,8}\) would be unaffected by these absorption interactions, and thus, antiviral activity may not be compromised.

Given the minor reduction in plasma APV AUC and lack of change in C\(_{12}\), FPV may be coadministered with antacids, such as MAALOX TC, without concern and without separation in dosing. The clinical significance of the moderate reduction in plasma APV AUC without a corresponding decrease in C\(_{12}\) following coadministration of FPV and ranitidine is unclear. Therefore, FPV and histamine\(_2\)-receptor antagonists should be coadministered with caution, because reduced plasma APV concentrations may result in a lowered virologic response. The impact of proton pump inhibitors on plasma APV pharmacokinetics following coadministration with FPV will be evaluated in a future study. Until data are available, the combination of FPV and proton pump inhibitors should also be used with caution.

### Table 1. Plasma APV pharmacokinetic parameters and treatment comparisons

<table>
<thead>
<tr>
<th>Treatment or comparison</th>
<th>AUC(_{0-24}) (µg·h/ml)</th>
<th>AUC(_{\text{app}}) (µg·h/ml)</th>
<th>C(_{\text{max}}) (µg/ml)</th>
<th>C(_{12}) (µg/ml)</th>
<th>t(_{\text{max}}) (h)(^d)</th>
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<tr>
<td>FPV</td>
<td>20.67 (17.31–24.69)</td>
<td>22.05 (18.50–26.30)</td>
<td>4.73 (4.11–5.45)</td>
<td>0.32 (0.25–0.40)</td>
<td>1.50 (0.75–5.00)</td>
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<tr>
<td>FPV + MAALOX TC</td>
<td>16.98 (14.32–20.14)</td>
<td>18.71 (15.72–22.26)</td>
<td>3.09 (2.69–3.54)</td>
<td>0.36 (0.28–0.48)</td>
<td>1.50 (0.75–5.00)</td>
</tr>
<tr>
<td>FPV + ranitidine</td>
<td>14.45 (11.46–18.22)</td>
<td>16.03 (12.55–20.48)</td>
<td>2.31 (1.86–2.87)</td>
<td>0.32 (0.24–0.42)</td>
<td>1.75 (0.75–5.00)</td>
</tr>
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</table>

\(a\) All data are based on results for a group of 26 subjects, except for the AUC\(_{\text{app}}\) data, which are based on a group of 24 because \(k\text{\_app}\) \(90\%\) CI in parentheses. \(b\) For all treatment data except \(t_{\text{max}}\) values, geometric means are given with \(95\%\) CIs in parentheses. \(c\) For all comparison data except \(t_{\text{max}}\) values, geometric least-squares mean ratios are given with \(90\%\) CIs in parentheses. \(d\) The \(t_{\text{max}}\) treatment and comparison data are expressed as medians with ranges in parentheses and least-squares mean ratios with \(90\%\) CIs in parentheses, respectively.

### References


