Protease Inhibitors and PPIs

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Proton pump inhibitors (PPIs) are the most potent inhibitors of gastric acid secretion currently available. They have become the treatment of choice for acid-related upper gastrointestinal (GI) symptoms and diseases. In addition to the classical indications for PPI therapy, some drug regimens produce a high incidence of GI side effects. For example, in a survey of HIV patients receiving highly active antiretroviral therapy, a majority reported using some sort of acid suppressive therapy including antacids, histamine-2 receptor antagonists (H_2RAs), and PPIs for heartburn and gastroesophageal reflux disease.[1] Thus, the potential for drug interactions between antiretroviral drugs and acid suppressive therapy is large. In this review, we will focus on the interactions between protease inhibitors and PPIs.

Atazanavir appears to be most sensitive to pH changes caused by PPIs. Studies have noted marked reductions in atazanavir area under the plasma concentration-time curve (AUC) when it is administered with PPIs including omeprazole and lansoprazole.[2-4] Atazanavir minimum plasma concentrations in patients treated with PPIs have been reported to be unaffected by concomitant PPI use.[5] The differences in these reports may be due to different subject types, PPI doses, and small sample sizes. Pending further data, PPIs should be avoided in patients taking atazanavir.

Fosamprenavir is a prodrug for amprenavir. Its solubility is reduced when the pH exceeds 3.3. One might expect PPIs would reduce its absorption. Studies where fosamprenavir is administered simultaneously with esomeprazole, however, did not detect a significant reduction in amprenavir plasma concentrations. It may be that administering the fosamprenavir at the nadir of the PPI's acid-suppressing action limits the potential effect. It is common for the gastric pH to drop below 3 during the morning before the effects of the PPI are maximized. It is noteworthy that H_2RAs produce a greater (30%) reduction in amprenavir concentrations, perhaps due to their more rapid effect on gastric pH after dosing. PPIs may produce a larger effect on fosamprenavir's absorption under different dosing conditions.

Omeprazole has been reported to reduce the plasma concentration of indinavir by up to 50%.[6,7] Increasing the dose of omeprazole from 20 to 40 mg daily increased the magnitude of the reduction.[7] Nelfinavir appears to be affected to a slightly lesser extent.[8]

Whereas darunavir, lopinavir, ritonavir, and tipranavir appear to be minimally affected by PPI administration, the plasma concentration of saquinavir has been noted to *increase* significantly during concurrent PPI dosing.[9,10] The administration of omeprazole 2 hours prior to the saquinavir dose produced a similar increase in the AUC (67% vs 54%), compared with simultaneous administration.[10]

It appears that the effects of PPIs on protease inhibitors (both decreased and increased plasma concentrations) are based on changes in gastric pH. The effects of H_2RAs typically mirror the changes noted with PPIs. Unfortunately, many of the studies did not measure gastric pH or control for differences in PPI metabolism due to CYP2C19 genotype. The clinical significance of the reported changes in protease inhibitor plasma concentrations remains to be defined. Reduced efficacy or the development of resistant strains of HIV may result from lowered plasma concentrations.

Due to the limited number of published studies often involving small numbers of healthy subjects, the mean changes in protease inhibitor concentration should be used only as a rough estimate of the magnitude of effect in a specific patient. It is probable that PPI-induced changes in protease inhibitor AUC will vary by specific PPI, its dosage regimen, pharmacogenetics, and a patient's underlying diseases. Patients taking protease inhibitors should be counseled regarding the use of acid-reducing drugs, including those available over the counter. If acid-reducing drugs are used, patients should be monitored for changes in their response to antiviral therapy. ■

Effect of PPIs on Plasma Concentrations of Protease Inhibitors

Protease Inhibitor	Mean Change in AUC (%)
Atazanavir (Reyataz)	Decrease 76-98
Darunavir (Prezista)	Increase 4
Fosamprenavir (Lexiva)	Decrease 2-9
Indinavir (Crixivan)	Decrease 10-50
Lopinavir/Ritonavir (Kaletra)	None
Nelfinavir (Viracept)	Decrease 36
Ritonavir (Norvir)	Decrease 0-17
Saquinavir/Ritonavir (Fortovase)	Increase 54-82
Tipranavir (Aptivus)	None

AUC = area under the plasma concentration-time curve; PPIs = proton pump inhibitors.

For a list of references, go to www.PharmacyTimes.com.