pH-Dependence of Atazanavir Intestinal Absorption and Its Drug-Drug Interactions with Acid-Reducing Agents

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Purpose
HIV protease inhibitor, atazanavir, demonstrates high variability in clinical pharmacokinetics, and its bioavailability is also sensitive to food intake and co-administration of acid-reducing agents (e.g., omeprazole, cimetidine). These interactions could be mediated by changes in gastrointestinal pH. However, to date little is known about the mechanisms involved in the pH dependent absorption of atazanavir or contribution of other factors (e.g., transport, metabolism) to these interactions.

Methods
Atazanavir permeability across Caco-2 cell monolayers (P_{app}) was evaluated in buffers of varied pH (4.5-8.5), in the fasted or fed-state simulated intestinal fluid, or at constant pH in the absence or presence of acid-reducing drugs and/or efflux inhibitors. The effects of pH, food intake and omeprazole on in situ permeability (P_{eff}) of atazanavir was assessed by single-pass perfusion in rat jejunum and ileum.

Results
In Caco-2 cells, atazanavir net accumulation and apical-to-basolateral P_{app} were higher at acidic pH4.5 compared to pH8.5 (p < 0.001). Increased accumulation of atazanavir at acidic pH appeared to be resulting from lower atazanavir efflux by P-glycoprotein and this effect was potentially related to the decrease in atazanavir lipophilicity and ability to permeate into the lipid bilayer observed at acidic pH. In situ permeability of atazanavir was also enhanced at acidic luminal pH, with 2.7 and 2.3-fold lower steady-state P_{eff} (p < 0.001) observed across rat jejunum and ileum, respectively, when pH was increased from 4.5 to 8.5. Fed-state buffer (pH 5.0) also enhanced atazanavir intestinal permeability compared to fasted-state buffer (pH 6.5), with higher apical-to-basolateral P_{app} (p < 0.001) and increased in situ P_{eff} coefficients (p < 0.05). Omeprazole moderately inhibited atazanavir efflux from Caco-2 cells at high concentrations; however, this effect was not observed in situ.

Conclusion
Atazanavir intestinal permeability is sensitive to changes in luminal pH. Decrease in pH and release of bile following food intake may contribute to the clinically reported increase in atazanavir absorption when taken with food. Even though some acid-reducing, such as omeprazole, can inhibit P-glycoprotein-mediated efflux of atazanavir in vitro, their pharmacological effect on the pH of gastrointestinal fluid appears to be responsible for the observed clinical atazanavir drug-drug interactions.

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