Emerging Issues: Co Administration of Acid-Reducing Agents in PI Therapy: An Expert Pharmacist’s Perspective

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INTRODUCTION

Most patients who start antiretroviral therapy will, at some point, probably suffer from acid-related conditions such as heartburn. In all likelihood, they will reach for an over-the-counter (OTC) antacid, a H2 blocker (H2B) (e.g. ranitidine), or a low-dose proton pump inhibitor (PPI) (e.g. omeprazole). At some point, these patients may also request a stronger, prescription product to alleviate their symptoms. The use of these prescribed medications makes it easy for the clinician to remember what their patients are taking to reduce acid production. However, what about OTC products or even home remedies? Chances are, not all patients will think of disclosing their use of these medications with their physicians.

The widespread use of these acid-reducing agents (ARAs) may directly impact the positive benefits achieved from highly active antiretroviral therapy (HAART). Specifically, drug-drug interactions between antiretrovirals and ARAs may produce significant decreases in plasma concentrations, particularly for some protease inhibitors (PIs). The gastric acidity of the stomach reduced by ARAs may, indeed, be required for the optimal absorption of a specific antiretroviral. This “catch-22,” if you will, is now becoming an emerging issue faced by patients and their caregivers. As will be described shortly, the high frequency of self-reported use of agents that affect gastric pH among HIV-infected patients underscores the need for increased patient education regarding the concomitant use of these products. Their effect on antiretroviral absorption may also have implications when it comes to selecting appropriate HAART regimens. This newsletter examines the current pharmacokinetic (PK) data available on this issue and identifies the need for further investigation into this growing problem.

SELF-REPORTED USE OF ACID-REDUCING AGENTS

A recent survey of HIV-infected patients points to widespread use of pH-altering medications, including OTC antacids, H2Bs, and PPIs. Conducted by Luber et al, the study surveyed 200 patients currently receiving HAART.1 Each had access to the Internet and had previously participated in an established chronic illness sufferers’
The participants accessed a prospective, interactive survey and answered questions about their use of antiretrovirals, the frequency of adverse events, and the use of ARAs. In order to help patients properly identify medications they had past or currently taken, photos were displayed of all FDA-approved antiretrovirals and ARAs. Since starting HAART, a large number of surveyed patients reported experiencing heartburn (62%), gastroesophageal reflux disease (GERD) (30%), and peptic ulcers (13%). In terms of managing these conditions, more than half (56%) took OTC medications exclusively. A high percentage of patients (39%) used both OTC and prescription agents to control excess acid production. Only a small minority (5%) was taking prescription drugs alone. During the past year, 88% of PPI users remained on therapy for more than 8 weeks. No differences were observed in the frequency and use of acid reducing agents between patients receiving protease inhibitor (PI)-based and non-PI-based HAART. It should be recognized that the population surveyed might not be representative of other populations being cared for by clinicians across the country. In this study, participants were affluent, gay white males. Conversations held with health care providers at inner city clinics paint a far different picture. Patients receiving treatment at these clinics often rely on prescriptions, including for OTC ARAs, given limited funds and state assistance for these medications. In this setting, clinicians are more likely to know what the patient is taking.

**PHarmacokinetic Considerations**

**Gastric Acidity**

Acid-reducing agents alter gastric acidity; hence their value in treating these various acid-related conditions. Creating a less acidic environment is in direct opposition to the needs of many PIs, which require acidic surroundings for optimal drug dissolution and absorption. When used concomitantly, acid-reducing agents and some PIs have the potential to produce negative drug-drug interactions. Subtherapeutic plasma levels of PIs could result in treatment failures.

**Enhancement and Dose Adjustment**

Low-dose ritonavir (RTV, Norvir®) is frequently used as a PK enhancer to increase plasma levels of other PIs. Under some circumstances, the increases in PI plasma concentrations observed may help overcome negative drug interactions. However, some PIs rely quite heavily on gastric pH for dissolution prior to absorption. In these instances, boosting with low-dose RTV may not enhance PI plasma drug levels because the drug is not soluble enough to be absorbed. For example atazanavir (ATV, Reyataz®) experiences significant reductions in area under the concentration-time curve (AUC) and in trough plasma concentrations ($C_{\text{min}}$) when given with antacids and proton pump inhibitors. Various efforts aimed at compensating for these changes, including low dose RTV and the use of coca-cola (for short-term decreases in gastric pH when taken concomitantly with ATV), have shown minimal affects in countering the negative drug interactions observed when ATV is given with these agents.
Factors Affecting PI Drug Absorption

A number of critical factors will determine the extent to which a PI is absorbed into the blood stream from the gut. While gastric acidity is a key factor, the rate of gastric emptying, amount of blood flow to the site of absorption, the ionizability, solubility, and lipophilicity of the PI and the presence or absence of food, among others, play key roles. These differences between PIs, as well as interindividual gastric pH responses to PPIs and H2 blockers, may partially explain why clinical failures among patients taking some PIs and ARAs in clinical practice have not been noted to date.

As mentioned above, the ability of a PI to be absorbed depends on its solubility, ionization and lipophilicity. In general, in order to be dissolved, weak bases need an acidic environment and weak acids need a basic environment. For example, the solubility of drugs that are weak bases will be decreased in the presence of agents that increase intraluminal gastric pH (e.g. H2 blockers, PPIs). However, in order for the PI to be absorbed, it is best to be non-ionizable and lipophilic. In an acidic environment, weak acids are non-ionized and in a basic environment, weak bases are non-ionized.

An additional cause of decreased absorption is the binding of divalent cations of antacids and sucralfate to PIs that are ionized thereby resulting in poorly absorbed complexes (also known as chelation). An additional cause of decreased absorption is the binding of divalent cations of antacids and sucralfate to PIs that are ionized thereby resulting in poorly absorbed complexes (also known as chelation). An additional cause of decreased absorption is the binding of divalent cations of antacids and sucralfate to PIs that are ionized thereby resulting in poorly absorbed complexes (also known as chelation).

The degree of effect of ARAs on the solubility and absorption of the various PIs is not fully understood. At one end of the spectrum is atazanavir (ATV, Reyataz), which is formulated as a acidic salt and could be more susceptible to changes in gastric pH and at the other end is lopinavir/ritonavir (LPV/r, Kaletra®) which is a non-ionizable compound and may be less susceptible to changes in gastric pH.

Measuring Drug Levels

In the best situation, the drug interactions between PIs and ARAs would be performed in a formal pharmacokinetic study in which serial PI blood levels were taken from patients receiving the PI in the presence and absence of the ARA. Unfortunately, many of these drug interaction studies are currently lacking. As a result, a number of recent reports have focused on a random single blood level from patients receiving PIs in combination with ARAs in clinical practice.

These data need to be interpreted with caution for a number of reasons: 1) wide interpatient variability exists among patients receiving the same PI. As a result, the level that is being observed may be low not because of a negative drug interaction but rather as a result of this interpatient variability; 2) the level that is being observed reflects the last few doses the patient has taken. If taken with the wrong food requirements or the patient did not take the last few doses at the appropriate time intervals (or the sample is drawn late), the PI level could be “low.” In addition, the level could be “therapeutic” but the patient may not have taken the PI with ARAs in the last few doses; 3) recent reports have shown wide intra-patient variability in PI levels over time. This may reflect the real world nature of these agents when given in clinical practice. As a result, if possible, it is best to do a number of levels over a few different days before making any clinical decision to ensure that the level is reproducible and 4) the level is only as good as the methodology of the laboratory performing the test. As a result, it is critical for clinicians to select a reliable laboratory where good quality...
assurance/quality control measures are implemented.

INTERACTIONS BETWEEN ARAs AND PIs

Atazanavir

Initial pharmacokinetic drug-drug interaction studies with ATV and antacid buffered didanosine showed a significant negative drug interaction with the AUC, Cmax, and Cmin of ATV being lowered by 87%, 89%, and 84%, respectively (these findings do not occur when the enteric coated formulation of ddI was used.4

Bristol-Myers Squibb recently presented pharmacokinetic data (Table 1) evaluating the drug interaction between ATV and omeprazole (previously released as a “Dear Health Care Provider”).5, 6 ATV 300 mg/RTV 100 mg QD was given for 10 days alone and then in combination with 40 mg of omeprazole (given 2 hours before ATV/RTV dose) to 48 healthy volunteers; the concomitant administration of omeprazole decreased ATV AUC, Cmax, and Cmin by 76%, 72%, and 78%, respectively. Two techniques used to try to compensate for altered ATV exposure levels proved to be of no benefit. These were increasing the ATV dose from 300 mg to 400 mg and giving 8 ounces of cola at the time ATV was taken. Consequently, the concomitant use of ATV (alone or boosted with low dose RTV) and PPIs are contraindicated. Studies are currently underway evaluating the OTC dose of omeprazole (20mg) in combination with ATV.

Farthing and Khanlou investigated the impact of PPIs and H2Bs on boosted and unboosted ATV trough levels among patients receiving ATV in 10 clinics in Los Angeles.7 Electronic medical records identified 50 patients and their medical providers asked to obtain an ATV trough level. Ultimately, levels were obtained on 15 patients taking PPIs and 20 patients receiving H2Bs. The researchers used an ATV trough value of 0.27 mcg/mL as the minimum ATV trough concentration for wild-type virus.

Among the 15 patients receiving PPIs, 6 had measured ATV trough levels below 0.27 mcg/mL. Four of the 20 patients taking H2Bs had ATV trough levels below the minimum of 0.27 mcg/dL. Of note, 5 of the 6 in the PPI group and 2 of the 4 in the H2B group with below minimum ATV trough levels were receiving RTV-boosted ATV. Proton pump inhibitors appeared to have a greater effect at lowering ATV trough levels below the minimum definition compared to H2Bs.

Studies investigating drug-drug interactions between ATV and H2Bs are ongoing and should be presented in the near future. Until the results are in, clinicians are wise to be prudent when using ATV with H2Bs and to follow the recommendation contained in the package insert.

### Table 1. PK Results for ATV/PPI (omeprazole 40 mg) Interaction Study

<table>
<thead>
<tr>
<th>Result</th>
<th>ATV/r 300/100 + PPI 40 QD</th>
<th>ATV/r 300/100 + PPI 40 + 8 oz Cola QD</th>
<th>ATV/r 400/100 + PPI 40 QD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmin</td>
<td>0.279</td>
<td>0.337</td>
<td>0.437</td>
</tr>
<tr>
<td>% Reduction</td>
<td>72</td>
<td>66</td>
<td>56</td>
</tr>
<tr>
<td>AUC</td>
<td>0.240</td>
<td>0.301</td>
<td>0.394</td>
</tr>
<tr>
<td>% Reduction</td>
<td>76</td>
<td>70</td>
<td>61</td>
</tr>
<tr>
<td>Cmax</td>
<td>0.223</td>
<td>0.271</td>
<td>0.345</td>
</tr>
<tr>
<td>% Reduction</td>
<td>78</td>
<td>73</td>
<td>66</td>
</tr>
</tbody>
</table>

“Reduced plasma concentrations of ATV are expected if H2Bs are administered with ATV. This may result in loss of therapeutic effect and development of resistance. To lessen the effect of H2Bs on ATV exposure, it is recommended that an H2B and ATV be administered as far apart as possible, preferably 12 hours apart.”

The idea for separating H2B and ATV by 12 hours is based on gastric pH changes observed for these ARAs. As the 12-hour mark approaches, gastric pH goes back down and may be sufficient enough to allow for ATV dissolution and subsequent absorption.

**Lopinavir/Ritonavir**

Bertz and colleagues retrospectively assessed the effect of ARAs on LPV/r plasma concentrations in patients with HIV infection who participated in a clinical trial evaluating QD vs. BID LPV/r (in combination with tenofovir DF/emtricitabine); this trial evaluated LPV trough concentrations at various time points throughout the 48-week study. Utilizing the concomitant medication list collected at each study visit, investigators evaluated LPV trough concentrations among subjects receiving ARAs and those not receiving ARAs. Investigators reported concurrent administration of ARAs in approximately 9% of patients in the QD arm and 10% in the BID arm. No reductions in LPV trough concentrations were observed in patients receiving/not receiving ARAs at various time points throughout the 48 week-study (Table 2).

These data suggest no significant interaction between ARAs and LPV and may be partially explained by the non-ionizable nature of the compound. It should be recognized, however, that these data are observational evaluations of trough concentrations throughout the study and are not from formal crossover pharmacokinetic trials (which are currently underway).

**Fosamprenavir**

Ford et al conducted a study to determine the effect of antacids and ranitidine on the single-dose PK of FPV. Fosamprenavir is the phosphate ester prodrug of APV. This was an open-label, randomized, three-way, balanced, crossover study; 26 healthy volunteers participated and were randomized into 3 treatment groups:

- FPV (1400 mg) alone
- FPV (1400 mg) immediately following MaaloxR TC (MLX) 30 mL
- FPV (1400 mg) taken 1 hour after ranitidine (ZantacR, ZAN) 300 mg

Ranitidine was given 1 hour prior to FPV in order to maximize the gastric pH at the time FPV was given as well as throughout its period of absorption. Maalox TC was taken at the same time as FPV in order to maximize the divalent metal cation load.
delivered to the gut at the time FPV was being absorbed.

The systemic exposure of APV (AUC) decreased 18% when FPV was given with Maalox TC and 30% when given with ranitidine. No effect with either ARA was observed on plasma APV C12 concentrations. Table 3 shows the plasma APV PK parameter treatment comparisons from data obtained on blood samples collected up to 24 hours post-dosing.

Table 3. Plasma APV PK Parameter Treatment Comparisons

<table>
<thead>
<tr>
<th>Comparison Ratio</th>
<th>( \text{AUC}_{0-24} ) (µg*h/mL)</th>
<th>( C_{\text{max}} ) (µg/mL)</th>
<th>( C_{12} ) (µg/mL)</th>
<th>( T_{\text{max}} ) (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPV+MLX:FPV</td>
<td>0.92 (0.74-0.91)</td>
<td>0.65 (0.57-0.76)</td>
<td>1.14 (0.91-1.39)</td>
<td>1.18 (0.84-1.39)</td>
</tr>
<tr>
<td>FPV+ZAN:FPV</td>
<td>0.70 (0.63-0.78)</td>
<td>0.49 (0.42-0.57)</td>
<td>0.99 (0.81-1.21)</td>
<td>1.37 (1.03-1.71)</td>
</tr>
</tbody>
</table>

*\( T_{\text{max}} \) treatment comparison expressed as LSM ratio (90% CI)

Clinicians can safely use FPV in combination with Maalox TC without dose adjustment or dose separation. The small gastric acid changes observed with antacids revert quickly. Such changes, coupled with the chelation effect of antacids, appear not to be clinically significant for APV.

In the case of FPV and ranitidine, the AUC is affected but not the \( C_{\text{min}} \). While a negative interaction was observed, it needs to be taken in context to the clinical situation. When given with low dose RTV, APV concentrations are increased roughly 6-fold as compared to unboosted FPV; as a result, a 30% reduction in APV exposures still results in levels well in excess of those observed with unboosted APV and are well above levels needed for wild-type virus. It should be recognized that these data come from single dose studies and need to be validated when FPV concentrations are at steady state. Studies are currently underway evaluating FPV alone and in combination with RTV (both BID and QD) with PPIs and should be available for presentation soon.

**CONCLUSION**

Despite the data already obtained for the studies discussed here, there remain considerable gaps in our knowledge when it comes to these drug-drug interactions. Several studies currently underway will build upon this existing information and further elucidate the factors responsible for these phenomena. Such studies will also either confirm present cautionary recommendations or lessen the seriousness of this issue. Future insights will depend heavily on well-designed pharmacokinetic data and from widespread use of these combinations in clinical practice.

Clinicians interested in conducting their own therapeutic drug monitoring of PIs in patients receiving ARAs should abide by some simple rules to make certain they obtain usable results (Table 4). A patient may receive insurance reimbursement for this testing; in some cases, a letter from the physician may be required.

Table 4. Recommendations for Therapeutic Drug Monitoring

- Obtain samples collected on more than one day to confirm clinical observation
- Time collection visit prior to next dose for trough concentrations
- Prepare and ship sample according to lab’s instructions
- Send sample to a reputable and experienced lab
- Be sure patient has not taken dose just prior to showing up
- Make certain patient is adherent and taking medications the correct way at the same time each day

If feasible, trying to obtain more than one plasma trough level may help identify what
is going on with the patient prior to any clinical decision-making. In the best situation, levels obtained before the concomitant administration of both agents would be most useful. For example, if a patient is receiving a PI-based HAART regimen and you wish to initiate a PPI, obtaining trough PI concentrations before and after the initiation of the PPI would help to determine if there is any impact on exposure levels. It is also critical for clinicians to evaluate all potential causes of low drug exposures prior to changes in therapy; these include patient adherence, incorrect food requirements, negative drug-drug and drug-herb interactions, and incorrect dosing intervals by the patient, among others. Finally, clinicians should only use laboratories that they know are reliable and utilize good quality assurance/control measures. One laboratory instrumental in developing PI assays is the Infectious Diseases Pharmacokinetics Laboratory at National Jewish Medical & Research Center, Denver, Colorado (www.njc.org/lab/idpl.html).

Clearly, both pharmacologists and clinicians need additional data from future studies to clarify many of these issues. Some of this new data will be released shortly. In the meantime, clinicians can benefit from an ongoing association with a pharmacist who can serve as a reference point for future findings and advice on current clinical decision-making. Likewise, those in the pharmacology world will find insight and perspective regarding these studies from a clinician’s point of view. Further effort will continue to require this team approach as these issues are answered fully.

REFERENCES


8. REYATAZ (atazanavir sulfate, Bristol-Myers Squibb) Package Insert.
