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Pharmacokinetics and pharmacodynamics in HAART and antibiotic therapy

Marta Boffito

St. Stephen's Centre, Chelsea and Westminster Hospital, London, UK

SUMMARY

Therapeutic agents used to inhibit the HIV replication are used in combination. The achievement of effective plasma concentrations of the drug in its active form, and sustaining such concentrations for the duration of a dosing interval without exceeding thresholds of toxicity is fundamental in HIV therapy. The issues determining the absorption, biotransformation, distribution to and activity at the intended site, and elimination, are myriad and complex. Studies at molecular, cell, and tissue levels are useful for predicting the possible fate of these agents *in vivo*, but the wide inter individual variability shown in whole-body pharmacokinetic studies is illustrative of the difficulty in making general statements rather than more guarded recommendations.

KEY WORDS: Antiretroviral drugs, Drug interactions, Pharmacology, HIV infection

INTRODUCTION

The long-term success of highly active antiretroviral therapy (HAART) depends on maintaining concentrations of active drug at the site of HIV replication sufficient to suppress viral replication and prevent the development of resistance. Although plasma concentrations of non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PI) have been correlated with virological outcome, there are persistent questions on the use of drug plasma concentration monitoring to guide treatment. Theoretically, the higher the trough concentration (measured at the end of the dosing interval), the better the inhibition of HIV (Boffito *et al.,* 2005).

However, precise therapeutic concentration ranges have not been identified for all antiretroviral drugs. Nucleoside reverse transcriptase inhibitors (NRTIs) are the current backbone of virtually all HAART combinations. NRTIs are prodrugs because the active moiety is the triphosphate anabolite that is formed intracellularly. NRTI-triphosphates elicit their anti-HIV effect via the inhibition of HIV reverse transcriptase, and presumably toxicity via the inhibition of mitochondrial DNA polymerase gamma. Therefore, the use of these compounds depends upon a quantitative understanding of the clinical pharmacology of intracellular NRTI-triphosphates (Anderson *et al.,* 2003).

Further, therapeutic drug monitoring is available only for NNRTIs and PIs. Before this test can be widely applied to routine antiretroviral therapy management, large scale clinical trials should ideally be completed to demonstrate its utility. However, this presents a considerable challenge and at the moment there are a series of clinical scenarios, such as hepatic impairment, in children, in women or in particular ethnic groups and during pregnancy, where therapeutic drug monitoring may be considered (Gazzard *et al.,* 2006). Importantly, drug concentrations alone are not the ultimate determinant of treatment outcome; other important factors include tolerability,

Corresponding author
Marta Boffito
Pharmacokinetic Research Unit
St. Stephen's Centre
Chelsea and Westminster Hospital
London, UK
E-mail: marta.boffito@chelwest.nhs.uk

safety, adherence, treatment history, and resistance profile.

DRUG-DRUG INTERACTIONS

Clinically relevant antiretroviral drug-drug interactions may occur among antiretroviral drugs belonging to the same or to different classes or between antiretroviral drugs and drugs received by HIV positive patients for the treatment of co-existing medical conditions, the treatment and prevention of opportunistic infections, for supportive care or for the limitation of adverse events caused by antiretroviral agents (Boffito *et al.,* 2005). It is worth noting that despite the well known mechanisms behind drug interactions involving NNRTIs and PIs (i.e. metabolism by cytochrome P450, CYP450, isoenzymes in the gastrointestinal tract and liver), other potential mechanisms involving such interactions are emerging (i.e. transporters, gastric pH-dependent absorption). Examples of important drug-drug interactions are reported below.

Protease inhibitors and statins

Metabolic disturbances associated with HIV infection and HAART are common. How best to treat these events is a pharmacological challenge because of the potential for clinically relevant drug-drug interactions associated with lipid lowering agents, such as HMG-CoA reductase inhibitors, also known as statins, and antiretroviral agents (Fichtenbaum *et al.,* 2002).

The primary route of metabolism for most statins is via oxidation utilizing the CYP450 3A4 pathway. Pravastatin, fluvastatin and rosuvastatin are exceptions since they follow different metabolic/elimination pathways. The lactone drugs, like lovastatin and simvastatin, which are administered as pro-drugs, are avid substrates for CYP3A4 and as such are inhibited by CYP3A4 inhibitors, which include the PIs and especially ritonavir (Fichtenbaum *et al.,* 2002).

Drug interaction studies have been performed with PIs and statins (Fichtenbaum *et al.,* 2002). Co-administration of saquinavir/ritonavir to HIV negative volunteers resulted in increased exposure to the active form of simvastatin by 3000%. Similarly, atorvastatin exposure increased by 343%, although the total atorvastatin activity (which includes the sum of atorvastatin and two of its active metabolites) increased by 79%. By contrast, pravastatin exposure declined by 50%. These data are of utmost clinical importance since all statins have the capacity for severe toxicity, including rhabdomyolysis and hepatic dysfunction.

Drug-drug interactions involving efavirenz

Metabolism induction by efavirenz may decrease PI exposure and therefore higher PI and/or ritonavir boosting dose may be necessary.

In fact, the recommended dose of lopinavir/ritonavir with efavirenz was 533/133 mg twice daily (addition of one capsule). Data on the dose of the new lopinavir/ritonavir formulation (tablet) that must be administered in the presence of efavirenz are unclear and further studies are needed (Kaletra 2006). The dosage regimen of boosted twice daily fosamprenavir/ritonavir (700/100 mg) does not require modification with efavirenz while the addition of 100 mg twice daily of ritonavir is recommended if fosamprenavir is used once daily (Lexiva 2006).

The effect of efavirenz on the pharmacokinetics of pravastatin, atorvastatin and simvastatin in HIV negative volunteers has also been studied and appeared to be safe (Fichtenbaum *et al.,* 2002). From a pharmacokinetic perspective, efavirenz is a potent inducer of simvastatin metabolism (leading to a 60% decrease in its plasma concentrations) and a less potent, but still significant, inducer of atorvastatin metabolism (35% decrease in exposure). Non-steady-state exposure of efavirenz did not change, this needs to be confirmed by steady-state data. Higher doses should be considered for simvastatin when co-administered with efavirenz.

It has been reported that efavirenz and nevirapine induce extensively the metabolism of methadone (Neuman *et al.,* 2006) and that tailoring the appropriate methadone coverage in efavirenz recipients can be problematic for the first few weeks of therapy. This has been recently confirmed in presence of the NRTI abacavir (also responsible for an accelerated methadone clearance), where the marked reduction in methadone concentrations was compensated by a methadone dose increase of approximately 30%, up to 60 weeks following antiretroviral initiation (Neuman *et al.,* 2006).

Protease inhibitors and gastric acid reducing drugs

Chemical factors can affect drug absorption by influencing the state of the drug in the gastrointestinal tract. The absorption of PIs is likely to be decreased in the absence of gastric acidity. Therefore, interactions between PIs and antiacid drugs are theoretically possible.

This is important since a prevalence of 49.8% of nausea/anorexia/upper gastrointestinal symptoms has been reported by a large national cohort study (Mathews *et al.,* 2000), and confirmed by a recent report investigating gastrointestinal acidity in HIV-infected subjects (Luber *et al.,* 2004). This suggests the frequent use of drugs able to control these symptoms, including anti-acidic drugs (H_2 antagonists, acid neutralizers and phosphate binders, proton pump inhibitors).

Available data suggest that there may be profound differences across PIs in terms of absorption dependence on gastric pH and, therefore, in terms of the influence that anti-acidic drugs may have on PI absorption.

Atazanavir and indinavir have been shown to exhibit significantly decreased absorption when given with anti-acid drugs. The area under the curve (AUC) and minimum concentration (C_{min}) of atazanavir (400 mg once daily) was reduced by 84 and 87% when administered with buffered didanosine (a didanosine formulation with cation chelating agents similar to Maalox) while the AUC of fosamprenavir (1400 twice daily) was reduced by only 18%, with no significant effect on C_{min}, by concomitant administration of Maalox. The deleterious effect of buffered drugs on atazanavir absorption may be counterbalanced by administering atazanavir two hours before or one hour after administration of these drugs, while for H_2 receptor antagonists (ranitidine) the two drugs should be administered as far apart as possible, e.g. 12 hours. Conversely, given the prolonged effect of the proton pump inhibitors and major decrease in atazanavir concentrations with these drugs, this interaction cannot be managed by separating atazanavir and the proton pump inhibitor doses.

In fact, a recent warning issued by the manufacturing company revealed that steady-state atazanavir C_{min} and AUC where 78 and 76% lower when atazanavir was administered at the standard dose of 300/100 mg once daily in association with 40 mg of omeprazole. Addition of 100 mg of atazanavir or eight ounces of cola where unable to compensate the effect of omeprazole on atazanavir absorption.

Co-administration of high dose ranitidine (300 mg) with fosamprenavir has been shown to decrease amprenavir AUC by 30% while the C_{min} was unchanged, suggesting a lack of effect of the higher gastric pH on trough concentrations. These data, however, was not confirmed by a multiple dose study investigating the interaction between esomeprazole, a potent proton pump inhibitor, and fosamprenavir (with and without ritonavir), where amprenavir plasma exposure was unchanged in the presence of esomeprazole (Shelton *et al.,* 2006).

More studies are needed to confirm which PIs can be administered in presence of an altered gastric pH and how this may impact plasma concentrations and therefore virological response. It has been argued that ritonavir boosting may not be capable of counterbalancing the effect of anti acidic drugs on PI availability. Therefore, this option should be thoroughly investigated as well.

CONCLUSIONS

The pharmacology of the different classes of antiretroviral agents is quite complex. Despite the expanded knowledge on the role of the hepatic CYP450 isoenzyme system in drug interactions, drug interactions are often unpredictable. Several different mechanisms can be responsible for interactions involving antiretrovirals, and these are complex and generally unclear.

Consequently, therapeutic drug monitoring could be considered in this setting to confirm that adequate (not too low or too high and therefore subtherapeutic or toxic) plasma concentrations are being achieved. There are numerous databases that list all specific drug interactions that have been observed in HIV clinical practice and that scientists believe may be likely.

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