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Editorial

Drug-drug interactions in HIV medicine: a not so simple and straightforward road to the future

Ritonavir is a well-known antiretroviral that has been extensively used in HIV therapeutics over the last 15 years. It is one of the first protease inhibitors to be developed and used in HIV-1 medicine. It is now rarely—if ever—used for its antiretroviral activity because it is associated with significant metabolic adverse effects such as hyperlipidemia [1,2]. On the other hand, ritonavir continues to be frequently used for its boosting effects in the plasma levels of other HIV drugs [3] by means of potent inhibition of both liver cytochromes and efflux transport proteins [4]. The downside is that numerous adverse interactions are possible when ritonavir is concomitantly used with other medications, and may even lead to potentially serious and/or life-threatening adverse events [5-7].

In this issue of the journal, Daali et al [8] report on the potential of a yet new interaction between ritonavir and the new antiplatelet prodrug prasugrel. Using recombinant microsomes, Daali et al found a potent inhibition of prasugrel bioactivation by ritonavir compared with other specific inhibitors of CYP3A and CYP2B6. This was attributed to the simultaneous inhibition of the aforementioned enzymes by ritonavir. This finding suggests a drug-drug interaction between these 2 medications that could prove to be clinically significant and needs to be studied further.

The problem of drug-drug interactions has become the subject of intense research in HIV therapeutics over the last decade. Various closely interdependent factors may affect the variability in the pharmacokinetics of an antiretroviral drug, including (*a*) medication-related factors (eg, other concomitantly administered medications, formulation of drug) and (*b*) host-related factors (such as age, sex, genetic factors, liver or other chronic disease, and environmental stimuli, like alcohol or nicotine exposure as well as dietary or nutritional habits). As an example, the dose of maraviroc (a new antiretroviral drug that acts through receptor inhibition) needs to be decreased if a liver enzyme inhibitor like ritonavir is used, or increased if a liver enzyme inducer like efavirenz (a nonnucleoside reverse transcriptase inhibitor) is used [9]. In addition, antiretroviral compliance has become one of the major issues in maintaining adequate viral and immunological control in HIV-1–infected patients. Over the last decade, there has been an increasing effort to simplify medicinal regimens and dosing schedules. However, patients frequently receive combinatorial regimens of medications belonging to at least 2 different classes of antiretrovirals even when initiating antiretroviral treatment [10]. The pharmacokinetics and pharmacodynamics of the various regimens used in HIV subjects are complex and lead to significant drug-drug interactions that are a very important part of day-to-day modern HIV management. The drugs effects in complex regimens may be very difficult to predict [11]. Efforts have been made to identify predictors of such interactions [12], and clinicians use specific web databases that describe potential or already published interactions between antiretrovirals and other regimens [13].

The therapeutic management of HIV-1–infected patients is further complicated by the need to manage other comorbidities that arise within the life span of HIV-infected patients. The HIV population with the advent of new drugs is increasingly getting older. The aging process is associated, on its own, not only with other comorbidities but also with important changes in the pharmacokinetics of various drugs [14,15]. Moreover, potential drug-drug interactions between antiretrovirals and other medications are increasingly examined at the specific disease level. Drug-drug interactions may not only have implications for the specific patient being treated at a given time but also have important public health implications such as in the case of malaria and HIV coinfection in Africa [16].

Metabolic issues as well as cardiovascular disease have emerged as important medical issues in the management of HIV-infected patients [17-19]. Novel therapeutic strategies for the HIV-associated metabolic syndrome are increasingly reported [20,21]. Preventive strategies have been implemented to address the metabolic syndrome observed in HIV patients and delay cardiovascular disease progression [22,23]. Prasugrel has been recently approved for use in patients with acute coronary syndromes undergoing primary coronary intervention to prevent thrombotic events [24]. Over the next years, it is anticipated that increasing numbers of HIV-1–infected patients will suffer from coronary heart disease and will undergo primary coronary intervention as a response to an emergent cardiac event [25-27]; such patients may require the new antiplatelet prodrug prasugrel as an antithrombotic agent and to prevent the recurrence of an ischemic event after the placement of stents in the coronary arteries. If such a patient is on a ritonavir-containing regimen and based on the findings of Daali et al, the serum concentrations of the active metabolite

(s) of prasugrel may be decreased, leading to a subtherapeutic effect. Nevertheless, it is difficult, given the early stage of current knowledge, to state with certainty whether ritonavir will definitely have a clinically important interaction with prasugrel in a significant number of patients. Although studies like the one by Daali et al are extremely important in understanding the potential interactions of various medications at the cellular level, more work should be done to elucidate and quantify clinically significant interactions at the patient level.

All pharmaceutical companies doing HIV research evaluate candidate drugs both at the preclinical and at the early clinical study level and attempt to characterize the metabolic profile of the medications including specific transporters and the enzymes involved in compound degradation. Such studies usually target the adequacy of antiviral drug levels as a factor critical in maintaining viral control. Phase I to III studies sometimes fail to recognize relatively rare but significant interactions that are eventually described during postmarketing studies. The complexity of the drug development process increases with the use of regimens that include medications prescribed for other comorbidities. Thus, significant toxicity issues arising from such interactions may not be discovered at all until an astute clinician identifies them. The outcome would of course be much better if, on the basis of pharmacology concepts, one would be aware of potential interactions and thus be watchful. The case of ritonavir serves as a good example of the numerous intricate difficulties in assessing such effects during drug development.

The future of drug-drug interaction studies goes beyond the basic research level. Carefully structured in vivo studies to examine dosing of drugs used for other conditions concomitantly with new antiretrovirals are both difficult and costly to perform. However, there are increasing reports of clinical studies in healthy volunteers such as 2- or 3-way crossover studies that evaluate the issue of drug-drug interactions for combinatorial regimens that include ritonavir and other medications [28]. The authors should be commented for continuing their research with a clinical protocol, details of which are already available (at: http://clinicaltrials.gov/show/NCT01346800). Nevertheless, basic science approaches such as the ones presented in the study by Daali et al establish the necessary background for clinical studies and push the way forward.

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