Correspondence

Unsuspected and Paradoxical Potential for Drug Interaction by Rifampin: Things to Ponder with Antiretroviral Therapy

To the Editor—In a review article recently published in the Journal, Dooley et al. [1] provided an in-depth examination of potential drug-drug interactions that may occur during use of combination antiretroviral therapy. The insights drawn by Dooley and colleagues and presented in the extensive literature citations documented in their review should provide guidance for the medical community, health care practitioners, pharmacists, and other clinical staff members to deal with the concurrent use of many of these agents during combination antiretroviral therapy, especially in developing and underdeveloped countries [1].

This correspondence is intended to provide additional perspectives on the relationships between (1) short-term switches in therapy, (2) other known clinical pharmacologic attributes of the agents relating to transporters (e.g., involvement of hepatic uptake phenomenon and biliary excretion of phase II conjugates), and (3) formation of active metabolite(s) that may impact pharmacological activity and decisions regarding which antiretroviral regimens should be administered to patients receiving treatment with other drugs.

Whereas the interplay occurring between cytochrome P450 (CYP) isozymes and transporters has been extensively reviewed by other researchers [2, 3], the unsuspected and paradoxical affects found in this interesting machinery recently documented in a few instances needs closer monitoring. The case in point is made with rifampin, which is commonly used in most of the underdeveloped and developing countries for other opportunistic infections that sets in this patient population. Rifampin is a well-established inducer of several CYP isozymes, as well as transporters (e.g., p-glycoprotein), in persons with chronic disease. It is generally well-known that co-administration of agents that are CYP3A/P-glycoprotein substrates with rifampin leads to reduced exposure of the agents. However, a single dose of rifampin has been shown to increase the exposures of dual CYP3A/transporter-modulated drugs, such as atorvastatin and bosentan [4, 5]. The underlying reason for this observation was the complete blockade of the hepatic transporter uptake (via the organic anion transport pathway) of these agents by rifampin [4, 5]. This unique attribute of rifampin has been extended to the inhibition of digoxin uptake in the in vitro isolated perfused rat liver model [6]. Other drugs have exhibited this property, most notably sildenafil. This drug showed a dramatic increase in the exposure of bosentan when the 2 agents were combined together for treating pulmonary arterial hypertension, which may be quite relevant to patients receiving long-term antiretroviral therapy [7]. Additionally, rifampin, owing to the inhibitory property of the organic anion transport mechanism, has been shown to interfere in the biliary excretion of ezetimibe and its glucuronides such that the exposures of these agents were drastically increased in a clinical setting [8]. Interestingly, the complexity and paradoxical nature of rifampin’s effect is well explained by the disposition of mycophenolic acid and its phase II conjugate metabolites (7-O-glucuronide and acyl glucuronide); although the exposure to the parent agent was drastically reduced, the glucuronides showed much greater systemic exposure, suggesting that an opposite interplay occurs during the dual CYP3A/transporter phenomenon [9]. Another area of particular importance relates to the contribution of active metabolite(s) toward antiretroviral efficacy. Here, attention is drawn to nelfinavir’s active metabolite, nelfinavir hydroxy-t-butylamide (M-8). Hirani et al. [10] documented CYP2C19 involvement in the formation of an active metabolite of nelfinavir, in relation to the homozygous phenotypes of CYP2C19. It has been suggested that inducibility of CYP2C19 in poor metabolizers by rifampin may be an important consideration for the optimization of antiviral therapy related to the use of nelfinavir, because it is interlinked to the accumulation of M8 metabolite.

Therefore, opportunity exists for ≥1 of the prescribed antiretroviral agents to show an unsuspected and paradoxical drug-drug interaction with rifampin. The existence of a drug-drug interaction by itself should not render the agents unusable. However, it adds a layer of complexity to perform risk-benefit analysis to ensure adequacy of dose size and frequency of dosing for the continuation of therapy. It also would provide a basis for therapy switch, if deemed appropriate.

To underscore the views expressed in this note, Dixit et al. [3] have unequivocally demonstrated induction of not only CYP isozymes but also efflux transporter systems in human hepatocytes by several protease inhibitors and provided some thoughts on the paradoxical nature of some interactions. Because there are a large number of unknown factors in this intriguing field, which involves scores of drug therapies on one hand and a complex immune/physiological system on the other hand, constant vigil and prudent choices of medications seem to be the main drivers for preventing drug-drug interactions in resource-limited regions.

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References


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Use of Mathematical Modeling to Inform Chlamydia Screening Policy Decisions

To the Editor—Regan et al. [1] predict that Chlamydia trachomatis prevalence in women in Australia will fall by >70% in 10 years with a screening program that tests 30% of 15–24-year-olds each year. This means that 70% of the target population would remain untested every year and that participants would be tested, on average, once every 3 years. This is an optimistic view of the impact that limited screening coverage would have, given the absence of evidence that opportunistic testing at this level has controlled chlamydia transmission up to now [2]. We think that there are reasons for caution in using predictions from this model to inform decisions on “the most effective chlamydia screening program for Australia” [1, p. 357].

First, the inability to model long-term partnerships explicitly in this compartmental model is a fundamental limitation...