Letters to the Editor

Comments on “Multiple Transporters Affect the Disposition of Atorvastatin and Its Two Active Hydroxy Metabolites: Application of in Vitro and ex Situ Systems”

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In response to the comprehensive study from Lau et al. (2006), I would like to point out that many of its findings, originating from experiments with in vitro (cell culture monolayers and rat liver microsomes) and ex situ (isolated rat liver) systems, do not conform well with results already obtained in humans. Thus, rifampicin (RMP or RIF) is presented as an inhibitor of MRP2, although it is an inducer of MRP2 in humans. For example, a 9-day treatment with RMP induced MRP2 mRNA and protein in human duodenum (Fromm et al., 2000). In a similar vein, the authors hypothesized that RMP might inhibit the P-glycoprotein (MDR1, ABCB1), although RMP is an inducer of MDR1 (Westphal et al., 2000). Furthermore, RMP is presented as an inhibitor of CYP3A-mediated atorvastatin (ATV) metabolism, even though it is well established that multiple doses of RMP markedly induce P450 enzymes, thereby considerably reducing the serum concentrations of various drugs that undergo P450-mediated metabolism. Accordingly, RMP (600 mg/day for 5 days) decreased the total AUC of atorvastatin by approximately 80% in healthy volunteers (Backman et al., 2005). The mechanism of this interaction is probably induction of the CYP3A4-mediated metabolism of atorvastatin by RMP, which contrasts with the authors’ conclusion that “Our study further confirms the dominance of [rat] Oatp in mediating the interactions between ATV and the Oatp inhibitor RIF.” Many typical P450 inducers actually behave like P450 inhibitors in acute studies with human liver microsomes, but such findings are not relevant to continuous drug treatment in clinical practice. In the study of Lau et al. (2006), in acute conditions, the AUC of atorvastatin was increased by RMP in the isolated perfused rat liver model. Caution is warranted when attempting to characterize mechanisms of drug disposition and drug-drug interactions in humans by means of in vitro cellular studies and animal studies.

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References


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ABBREVIATIONS: RMP/RIF, rifampicin; ATV, atorvastatin; P450, cytochrome P450; AUC, area under the curve; Oatp, organic anion-transporting polypeptide.