Drug interaction potential of high-dose rifampicin in patients with pulmonary tuberculosis

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Abstract:
Background. A growing body of evidence supports the use of higher doses of rifampicin for the treatment of tuberculosis (TB). Rifampicin is a potent inducer of metabolic enzymes and drug transporters, causing many clinically relevant drug interactions. Little is known about the maximal inductive capacity of rifampicin. To assess the drug interaction potential of higher rifampicin doses, we compared the effect of high-dose rifampicin (40 mg/kg daily, RIF40) and standard dose rifampicin (10 mg/kg daily, RIF10) on the activities of major cytochrome P450 (CYP) enzymes and P-glycoprotein (P-gp).
Methods. Twenty-five adults with pulmonary TB completed this open label, 1-arm, 2-period, fixed-order phenotyping cocktail study. All participants received RIF10 (days 1-15; period 1), followed by RIF40 (days 16-30; period 2). A single dose of an oral phenotyping cocktail of selective substrates (probe drugs) was administered on days 15 and 30: caffeine (CYP1A2), tolbutamide (CYP2C9), omeprazole (CYP2C19), dextromethorphan (CYP2D6), midazolam (CYP3A) and digoxin (P-gp). Intensive pharmacokinetic blood sampling was performed over 24 hours after probe drug intake. The total exposure (area under the curve, AUC) was determined for each of the probe drugs in both periods. The extent of additional induction attributable to RIF40 dose was assessed by point estimates and 90% confidence intervals (90%CI) for geometric mean (GM) RIF40/RIF10 AUC ratios.
Results. Geometric mean ratios (90% CI) of the total exposure (area under the concentration versus time curve, RIF40 versus RIF10) for each of the probe drugs were: caffeine, 105% (96-115%); tolbutamide, 80% (74-86%); omeprazole, 55% (47-65%); dextromethorphan, 77% (68-86%); midazolam, 62% (49-78%), and 117% (105-130%) for digoxin.
Conclusions. Metabolic phenotyping as a screening tool revealed that high-dose rifampicin resulted in no additional effect on CYP1A2, mild additional induction of CYP2C9, CYP2C19, CYP2D6 and CYP3A, and marginal inhibition of P-gp. These results suggest that existing recommendations on managing interactions with rifampicin can remain unchanged for many co-administered drugs when using high-dose rifampicin. Further interaction studies may be warranted, focussing on high-dose rifampicin and CYP3A or CYP2C19 substrates with a narrow therapeutic index.