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Model-Based Comparative Analysis of Rifampicin and Rifabutin Drug-Drug Interaction Profile

Vianney Tuloup,[a,b] Mathilde France,[a] Romain Garreau,[a,b] Nathalie Bleyzac,[a] Laurent Bourguignon,[a,b,c] Michel Tod,[a,b,c] Sylvain Goutelle[a,b,c]

[a]Hospices Civils de Lyon, Groupement Hospitalier Nord, Service de Pharmacie, Lyon, France
[b]Université Lyon, Université Lyon 1, UMR CNRS 5558, Laboratoire de Biométrie et Biologie Evolutive, Villeurbanne, France
[c]Université Lyon, Université Lyon 1, ISPB, Faculté de Pharmacie de Lyon, Lyon, France

ABSTRACT Rifamycins are widely used for treating mycobacterial and staphylococcal infections. Drug-drug interactions (DDI) caused by rifampicin (RIF) are a major issue. We used a model-based approach to predict the magnitude of DDI with RIF and rifabutin (RBT) for 217 cytochrome P450 (CYP) substrates. On average, DDI caused by low-dose RIF were twice as potent as those caused by RBT. Contrary to RIF, RBT appears unlikely to cause severe DDI, even with sensitive CYP substrates.

KEYWORDS rifampicin, rifabutin, drug-drug interaction, pharmacokinetics

Rifampicin (RIF [also known as rifampin]) is a first-line antimicrobial agent for various infectious diseases, such as tuberculosis (TB), brucellosis, and some staphylococcal infections, including infectious endocarditis and bone and joint infections. A major issue associated with rifampicin use is drug-drug interactions (DDI). Rifampicin is a potent inducer of several cytochrome P450 (CYP) and drug transporters, including P-glycoprotein (P-gP). Rifampicin may be responsible for strong DDI when coadministered with sensitive CYP substrate drugs (1). Rifabutin (RBT) is another rifamycin agent that shows a similar antimicrobial activity (2). It is considered an alternative to rifampicin for TB therapy (3, 4). In addition, increasing data suggest its potential for staphylococcal infections (2, 5–8). The induction potency of rifabutin is significant *in vitro* (9). However, rifabutin is considered a less potent drug inducer *in vivo* and should cause fewer strong DDI than rifampicin (10, 11), but comparative data are limited (12, 13). The aim of this study was to compare the magnitudes of DDI caused by rifampicin and rifabutin by using a modeling approach.

We used the *In vivo* Mechanistic Static Model (IMSM) implemented in the DDI-Predictor website (14–16) to calculate and compare the magnitudes of DDI caused by rifampicin (450 to 600 mg per day [RIF600]) and rifabutin (300 mg/day [RBT300]) for substrates of CYP3A4, CYP2C9, CYP2C19, and CYP1A2. The model implemented in the DDI-Predictor website has been previously validated for a large number of CYP substrates and interactors (17–20).

The metric used to quantify DDI magnitude was R_{AUC}, defined as the ratio of area under the concentration-time curve of the substrate drug coadministered with the inducer (AUC*) over that of the substrate drug alone (AUC). The IMSM model for CYP induction can be summarized as

$$R_{AUC} = \frac{AUC^*}{AUC} = \frac{1}{1 + \sum(CR_{CYP} \times IC_{CYP})} \quad (1)$$

where CR is the contribution ratio of each CYP in the drug oral clearance, ranging from 0 to 1, and IC is the potency of induction, ranging from 0 to $+\infty$ theoretically for each CYP involved. IC values estimated in a previous study (19) for rifabutin at 300 mg/day

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Address correspondence to Sylvain Goutelle, sylvain.goutelle@chu-lyon.fr.

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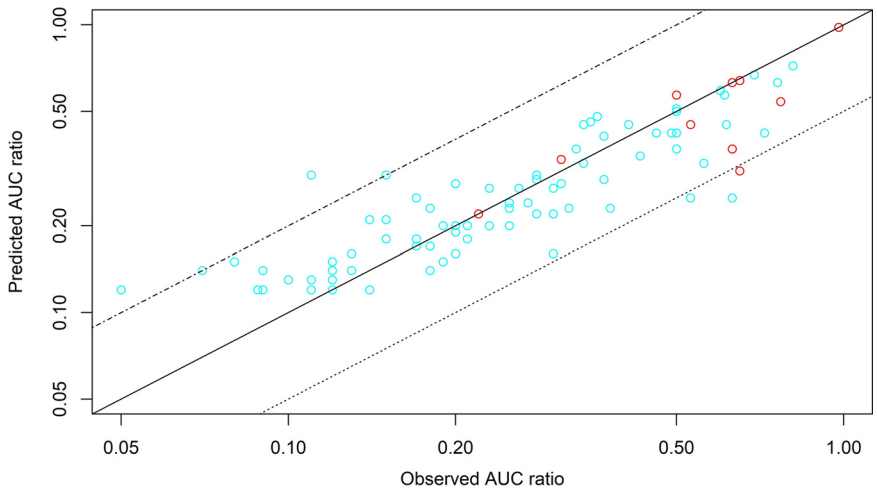

FIG 1 Predicted versus observed AUC ratio of substrate drugs for DDI caused by rifampicin and rifabutin reported in the literature. The solid line is the line of identity ($y = x$). The dotted line is $y = 0.5x$, and the combined dashed and dotted line is $y = 2x$. Abbreviations: RBT300, rifabutin at 300 mg/day (red circles); RIF600, rifampicin at 600 mg/day (cyan circles).

(RBT300) and rifampicin at 600 mg/day (RIF600) were 2.15 and 7.7, 0.67 and 1.22, 4.2 and 4.2, and 0.03 and 1.44 for CYP3A4, -2C9, -2C19, and -1A2, respectively. External validation of the model was performed by comparing the predicted R_{AUC} to observed data reported in the literature for DDI caused by the two drugs.

Then, we predicted the R_{AUC} for every drug recorded in the DDI-Predictor database, except those metabolized only by CYP2D6, as the activity of this CYP cannot be induced (17). The interactions were classified as weak ($0.5 \leq R_{AUC} \leq 1$), moderate ($0.2 < R_{AUC} < 0.5$), and strong ($R_{AUC} \leq 0.2$) (21). We compared the magnitudes of drug interactions caused by rifabutin at 300 mg/day (RBT300) and rifampicin at 450 to 600 mg/day (RIF600).

Detailed results of external validation are shown in the supplemental material. The supplemental material also provides data on CYP substrate drugs and other metabolism and transporter pathways (12, 13, 22–106). Figure 1 shows the plot of predicted versus observed AUC ratios. Model-based predictions correlated well with observed AUC ratios for both drugs.

Model predictions for 217 substrates of the DDI-Predictor database are summarized in Fig. 2. For RIF600 and RBT300, the median (with interquartile range in parentheses) R_{AUC} values were 0.22 (0.16 to 0.41) and 0.47 (0.36 to 0.61), respectively. On average, DDI caused by RIF600 were twice as potent than those caused by RBT300. Strong DDI were observed for 44% of substrates when coadministered with RIF600 and for only 1.05% of substrates when coadministered with RBT300. Moderate DDI were observed for 42% and 56% of substrates when coadministered with RIF600 and RBT300, respectively. Weak DDI were observed in 14% and 43% of cases with RIF600 and RBT300, respectively. Table 1 shows the proportion of DDI classified as strong, moderate, and weak when switching from RIF600 to RBT300, those dosages being considered equivalent, at least for TB therapy (107). The use of RBT300 instead of RIF600 would be associated with a lower magnitude of DDI for most CYP substrates.

As an illustration, Table 2 shows the predicted AUC for a selection of 10 CYP substrate drugs when coadministered with RIF600 and RBT300. We selected some substrates highly selective of a given CYP pathway and others with a multiple-CYP metabolism. Predictions for all 217 substrates are available on the DDI-Predictor website (https://www.ddi-predictor.org/).

Our model-based analysis confirmed that the magnitudes of DDI caused by rifampicin and rifabutin are quite different. Rifabutin at 300 mg/day has lower induction potency than the equivalent dosage of rifampicin (600 mg/day). Consequently, rifabutin

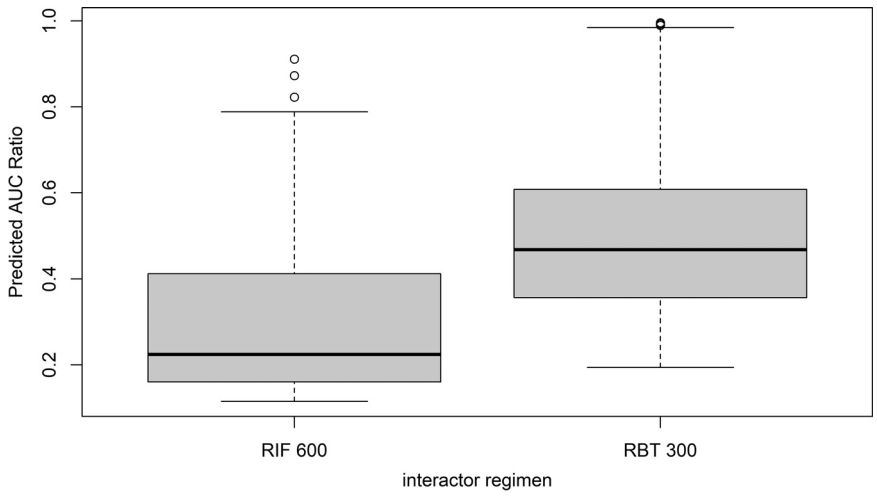

FIG 2 Box plot of predicted AUC ratios for 217 drug-drug interactions between CYP substrates and rifamycin agents. Abbreviations: RIF 600; rifampicin at 600 mg/day; RBT 300, rifabutin at 300 mg/day.

is associated with much lower proportions of severe and moderate DDI. Indeed, rifampicin is the most potent CYP inducer in the DDI-Predictor database, and its induction potency is even greater when used at a higher dose of 1,200 mg/day (13), which is common in the therapy of bone and joint infections. Our results suggest that rifabutin could be more convenient and safer than rifampicin regarding DDI. While the predicted AUC ratio could be used for dosage adjustment of substrate drugs when coadministered with rifamycin agents, strong DDI with a predicted AUC ratio of ≤ 0.2 would require very large dose increases, which raises safety concerns. Such strong DDI are usually considered contraindications. As rifabutin can only cause weak to moderate DDI, rates of drug switch or dose increases of the substrate drug would be lower.

This study has several limitations. Only CYP pathways are formally incorporated in the model (equation 1). This means that the CR parameters and AUC ratios may be less accurate for drugs with non-CYP pathways that are also altered by RIF or RBT. However, because our approach is only based on *in vivo* data, the influence of drug inducers on other pathways may be indirectly quantified and considered. Indeed, the model prediction correlates well with observations, even for drugs that are known substrates of transporters and enzymes other than CYP, as shown in Table S1 in the supplemental material. It is noteworthy that rifabutin is also a substrate of CYP3A4, unlike rifampicin. Therefore, coadministration with CYP3A4 inducers and inhibitors may alter rifabutin pharmacokinetics and its induction potency. We only considered one dosage of rifabutin in our predictions, because no data were available to derive estimates for other dosages. It is possible that higher dosages of rifabutin could result in a greater magnitude of DDI.

Further clinical evaluation is necessary to assess whether rifabutin can be a safe and effective alternative to rifampicin. However, our model-based analysis confirms that rifabutin has a more favorable DDI profile than rifampicin. Contrary to rifampicin, rifabutin appears unlikely to cause strong DDI (i.e., with an R_{AUC} of <0.2), even with sensitive CYP substrate drugs.

TABLE 1 Compared classification of DDI caused by rifampicin and rifabutin[a]

	No. (%) of DDI with RIF600	
DDI with RBT300	**Moderate ($n = 91$)**	**Strong ($n = 95$)**
Strong	0 (0)	1 (1)
Moderate	28 (30.8)	94 (99)
Weak	63 (69.2)	0 (0)

[a]RBT300, rifabutin at 300 mg/day; RIF600, rifampicin at 600 mg/day.

TABLE 2 Predicted AUC ratios of DDI for a selection of 10 CYP substrate drugs when coadministered with RIF600 and RBT300[a]

	CR of CYP to substrate oral clearance					Mean R_{AUC} (95% CI) with[b]:	
Substrate	CYP3A4	CYP2D6	CYP2C9	CYP2C19	CYP1A2	RBT300	RIF600
Acenocoumarol			0.99			0.60 (0.40–0.90)	0.45 (0.28–0.73)
Agomelatine					0.99	0.97 (0.73–1.29)	0.41 (0.25–068)
Gliclazide			0.24	0.76		0.23 (0.12–0.43)	0.22 (0.12–0.42)
Ibrutinib (fasting)	0.98					0.32 (0.18–0.56)	0.12 (0.06–0.23)
Lansoprazole	0.27			0.73		0.22 (0.11–0.40)	0.16 (0.08–0.32)
Oxycodone	0.54	0.2				0.46 (0.29–0.75)	0.19 (0.10–0.37)
Risperidone	0.25	0.75				0.65 (0.45–0.95)	0.34 (0.20–0.59)
Simvastatin	0.97					0.32 (0.19–0.57)	0.12 (0.06–0.24)
Tacrolimus	0.91					0.34 (0.19–0.59)	0.12 (0.06–0.25)
Vortioxetine	0.24	0.6		0.13		0.48 (0.30–0.77)	0.29 (0.17–0.53)
Warfarin S			0.99			0.60 (0.40–0.90)	0.45 (0.28–0.73)

[a]Abbreviations: CR, contribution ratio; CYP, cytochrome P450; R_{AUC}, ratio of AUC* to AUC; RIF600, rifampicin at 600 mg/day; RBT300, rifabutin at 300 mg/day.
[b]R_{AUC} values are given as the mean with 95% confidence interval (CI) in parentheses.

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 0.2 MB.

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N.B., L.B., M.T., and S.G. have contributed to the DDI-Predictor website, which is a free Web tool, without any profit for the authors. The authors have no conflicts of interest that are relevant to the content of this study.

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