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PHARMACOLOGY

Rifampicin Transport by OATP1B1 Variants

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ABSTRACT Single nucleotide polymorphisms in the OATP1B1 transporter have been suggested to partially explain the large interindividual variation in rifampicin exposure. HEK293 cells overexpressing wild-type (WT) or OATP1B1 variants *1b, *4, *5, and *15 were used to determine the *in vitro* rifampicin intrinsic clearance. For OATP1B1*5 and *15, a 36% and 42% reduction in intrinsic clearance, respectively, compared to WT was found. We consider that these differences in intrinsic clearance most likely have minor clinical implications.

KEYWORDS OATP1B1, SNP, drug transport, rifampicin

Tuberculosis (TB) is the leading cause of death from an infectious agent. In 2018, an estimated 10 million people developed TB and 1.45 million patients died (1). Rifampicin was first used clinically in 1966 and now is the keystone of TB treatment. Together with pyrazinamide, it enabled short-course TB chemotherapy (2). However, there is a large interindividual variability in the plasma pharmacokinetics (PK) of rifampicin (3), and low plasma concentrations of rifamycins (e.g., rifampicin and rifabutin) have been associated with treatment failure, relapse, and resistance (4). Both nongenetic factors (e.g., age, comorbidities, concomitant therapy) as well as genetic factors (e.g., sequence variants in genes encoding drug-metabolizing enzymes and transporters) contribute to this interindividual variability and influence the effect of TB drugs (5, 6).

The organic anion transporter polypeptide 1B1 (OATP1B1), located at the sinusoidal (basolateral) membrane of hepatocytes, mediates the uptake of a broad range of compounds, including rifampicin (7, 8). A large number of >45 nonsynonymous variants have been found in the solute carrier organic anion transporter gene (*SLCO1B1*) encoding OATP1B1 (9). Next to the wild-type haplotype, there are four common haplotypes resulting from three single nucleotide polymorphisms (SNP), which are summarized in Table 1. Their *in vitro* activity has been investigated for several (endogenous) substrates, often resulting in decreased activity, mainly for OATP1B1*5 and *15 (8, 10–14). The effect of SNPs on the transporter activity can be substrate specific (8), and therefore it is important to examine rifampicin-specific transport by OATP1B1 variants. Nonetheless, *in vitro* transport of rifampicin by different forms of OATP1B1 has only been investigated in one previous study, at only a single concentration, and therefore transport kinetics remain unknown (12). In clinical studies, decreased plasma exposure (~40%) has been observed in patients carrying OATP1B1*4, probably indicating increased transporter activity (15, 16). In contrast, OATP1B1*1b was not associated with altered rifampicin exposure, nor was OATP1B1*5 (15–17). Rifampicin plasma exposure data related to OATP1B1*15 were not found in literature, but the *15 haplotype did show a significant association between rifampicin and susceptibility to drug-induced liver injury (DILI) in a Chinese population. In the same study, the *in vitro* uptake of the bile acid taurocholic acid (TCA) in OATP1B1 was measured, showing decreased uptake of TCA in *15-expressing cells compared to wild-type cells. This

Citation Litjens CHC, van den Heuvel JJMW, Russel FGM, Aarnoutse RE, te Brake LHM, Koenderink JB. 2020. Rifampicin transport by OATP1B1 variants. Antimicrob Agents Chemother 64:e00955-20. https://doi.org/10.1128/AAC.00955-20.

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Received 12 May 2020
Returned for modification 10 June 2020
Accepted 13 July 2020
Accepted manuscript posted online 20 July 2020
Published 21 September 2020

TABLE 1 Literature overview of the tested haplotypes with corresponding nucleotide and amino acid changes, their allele frequencies in different ethnicities, residual *in vitro* activity for (endogenous) substrates (estrone-3-sulfate, estradiol-17β-D-glucuronide, pravastatin, atorvastatin, rosuvastatin, rifampicin), *in vivo* exposure to rifampicin, and transporter protein expression compared to OATP1B1 wild type *in vivo*[n]

			Allele frequency (%)					Residual activity		
Haplotype	Nucleotide change	Amino acid change	European	East Asian	Central/south Asian	American	Sub-Saharan African	(Endogenous) substrates – *in vitro*	Rifampicin exposure – *in vivo*	Protein expression (fold change) *in vivo*
*1b	388A>G	N130D	30–47[a,b]	59–86[a,b]	42–52[b]	55–71[b]	72–84[a,b]	↓ ↔ ↑ (~*35%–125%*)[c-h]	↔[i]	↑ (~*1.5*×)[k,l]
*4	463C>A	P155T	13–23[a,b]	0–3[a,b]	5–10[b]	0–6[b]	2–10[a,b]	↔[c,g,h]	↓ (58–65%)[i,j]	↑ (2.1×)[l,m]
*5	521T>C	V174A	8–20[a,b]	10–16[a,b]	7–13[b]	18–32[b]	1–8[a,b]	↓ (~*5%–80%*)[c-e,g,h]	↔[i,j]	↔ ↓ (~*0.75*×)[k,l]
*15	388A>G, 521T>C	N130D, V174A	16[b]	12[b]	9[b]	24[b]	2[b]	↓ (~*20%–55%*)[d,e]	?	↔[k,l]

[a]Niemi et al. (8).
[b]Pasanen et al. (14).
[c]Tirona et al. (11).
[d]Kameyama et al. (27).
[e]Nozawa et al. (28).
[f]Iwai et al. (29).
[g]Tirona et al. (12).
[h]Ho et al. (30).
[i]Weiner et al. (15).
[j]Kwara et al. (16).
[k]Nies et al. (31).
[l]Prasad et al. (22).
[m]Genotype-based (without regard to haplotypes).
[n]Arrows and percentages for the *in vitro* and *in vivo* activity represent the residual *in vitro* activity and *in vivo* plasma exposure of variants compared to wild-type OATP1B1 (set at 100%). For protein expression, the fold change relative to wild-type OATP1B1 is presented. Values in italic are the residual activity/fold change in protein expression compared to OAPT1B1 wild type, as far as they could be extracted from data presented in literature; for the activity, this is often measured at one concentration (i.e., no enzyme kinetics).

uptake could be further reduced by rifampicin acting as an inhibitor (18). Increased bile acids have previously been associated with drug-induced cholestasis and DILI (19, 20).

In this study, we aimed to identify the *in vitro* activity of OATP1B1 WT, *1b, *4, *5, and *15 for rifampicin transport. A detailed overview of the methods used can be found in the supplemental material file. In brief, human embryonic kidney 293 (HEK293) cells were transiently transduced with OATP1B1 WT, one of the SNP variants, or the vector control (i.e., background uptake). After confirmation of functional OATP1B1-mediated uptake with the model substrate [^{3}H]-estradiol 17 β-D-glucuronide ($E_2$17βG; 18.9 nM) for OATP1B1 WT, *1b, *4, and *5 (see Fig. S1 in the supplemental material), cells were incubated with [^{3}H]-rifampicin (46.6 Ci/mmol; Moravek Biochemicals, Brea, CA, USA). First, the time-dependent uptake of rifampicin in OATP1B1 WT was assessed, resulting in a linear (not saturated) uptake from 0 to 1 min (Fig. S2). Second, cells were incubated for 1 min with different concentrations of rifampicin (13.7 nM [^{3}H]-rifampicin supplemented with 0.015, 0.05, 0.15, 0.5, 1.5, 3, and 5 μM rifampicin). Due to the high lipophilicity of rifampicin, there was high uptake via passive diffusion. Therefore, 5 μM was the highest concentration that could be tested in our system. As a result, it was not possible to reliably determine the maximum transport velocity (V_{max}) and the substrate concentration at which half of this rate is obtained (K_m). Hence, the intrinsic clearance (CL_{int}, by definition, V_{max}/K_m, in our case determined with the slope of the linear part of the concentration-dependent uptake curve) was determined instead and used to compare the different OATP1B1 haplotypes. The mean intrinsic clearance was decreased to 64%, 51%, 49%, and 57% for *1b, *4, *5, and *15, compared to OATP1B1 WT, respectively (Table 2 and Fig. 1A). As a third step, we accounted for differences in transporter expression levels. Western blotting was performed using membrane fractions from the transduced HEK293 cells per virus batch using an equal amount of protein (25 μg). Proteins were separated on an SDS-PAGE gradient gel (4% to 20%), and OATP1B1 proteins were detected using a polyclonal anti-OATP2 antibody (1:1,000, which was a kind gift from B. Stieger, University Hospital Zurich, Zurich, Switzerland [21]) followed by an Alexa Fluor 680 goat anti-rabbit IgG secondary antibody (1:10,000; Life Technologies Invitrogen). The molecular mass of the glycosylated band was approximately 75 kDa; however, both the glycosylated and nonglycosylated band were

TABLE 2 Intrinsic clearance of rifampicin by different variants of OATP1B1[f]

Haplotype	CL_{int} (mean± SD, μl/mg protein/min)[a]	Relative transporter expression (mean ± SD, % of WT)[b]	Transporter expression corrected CL_{int} (mean ± SD, % of WT)[c]
OATP1B1 WT	11.3 ± 4.4	100	100
OATP1B1*1b	7.2 ± 2.7	77 ± 37	92 ± 30
OATP1B1*4	5.8 ± 3.3	68 ± 13	73 ± 18
OATP1B1*5	5.6 ± 2.7	78 ± 9	64 ± 14[d]
OATP1B1*15	6.5 ± 3.4	95 ± 41	58 ± 8[e]

[a]Slope of the concentration-dependent uptake curve based on the mean rifampicin uptake determined in three independent experiments.
[b]Transporter expression was determined and normalized to wild-type expression per independent experiment (i.e., three times), after which, the mean relative transporter expression per variant was calculated.
[c]Data per individual experiment were analyzed to determine the intrinsic clearance and normalized to the intrinsic clearance of the wild-type transporter per experiment. Subsequently, the CL_{int} values were normalized for the expression of OATP1B1 protein per individual experiment, determined by Western blotTIN, an example of which is shown in Fig. 2. Significance was tested by four one-sample *t* tests comparing the experimental group to the wild type (100%).
[d]$P = 0.04$.
[e]$P = 0.01$.
[f]SD, standard deviation.

used for quantification (Fig. 2). The mean expression levels of OATP1B1*1b, *4, and *5 were lower than OATP1B1 WT. Subsequently, intrinsic clearance values were normalized per experiment for the OATP1B1 protein expression, and significance was tested by four one-sample *t* tests comparing the experimental groups to the wild type (set at 100%). The mean normalized intrinsic clearance value of OATP1B1*5 and *15 were reduced to 64% ($P = 0.04$) and 58% ($P = 0.01$) of OATP1B1 WT, respectively, whereas the intrinsic clearance values of OATP1B1*1b and *4 were similar to OATP1B1 WT (Table 2, Fig. 1B).

The lack of a difference in intrinsic clearance between OATP1B1*1b and WT is in agreement with literature, where this haplotype has not been associated with differences in rifampicin exposure *in vivo* (15, 16). In contrast, the amino acid change P155T (*4) has been associated with ~40% lower rifampicin concentrations *in vivo* (15, 16). However, in this *in vitro* study, we did not observe an increased intrinsic clearance of rifampicin in OATP1B1*4-expressing cells compared to WT cells. Also, Tirona et al. did not find an increased activity of OATP1B1*4 in HeLa cells, although they studied only a single rifampicin concentration (12), nor was a difference observed in *in vitro* experiments of other (endogenous) substrates (8, 14). Prasad et al. reported that OATP1B1 expression in liver samples is about 2-fold higher in both the hetero- and homozygous c.463C>A (irrespective of haplotype) samples compared to CC samples (22). This increased transporter expression may be associated with decreased rifampicin plasma concentrations without a difference in observed transporter activity in our *in vitro* study.

We did find a reduction in intrinsic clearance for OATP1B1*5 (residual activity, 64%)

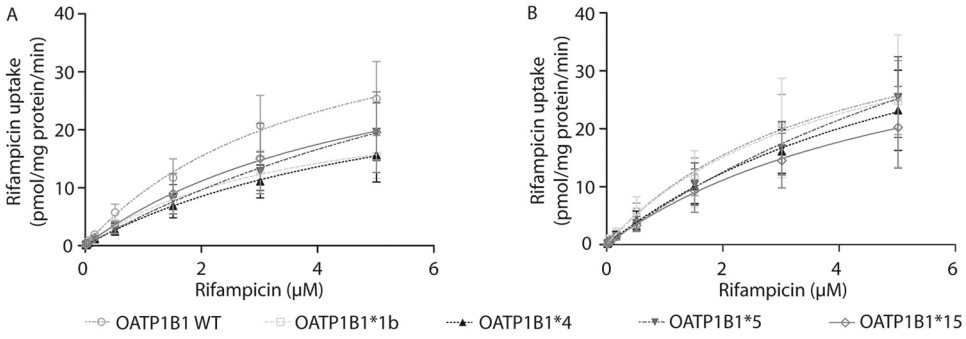

FIG 1 (A and B) Concentration-dependent uptake curve for OATP1B1-mediated uptake of rifampicin (A) and corrected for transporter expression by Western blotting (B). The transport velocity was determined by examining the uptake of rifampicin in OATP1B1 WT, *1b, *4, *5, and *15. The OATP1B1 mediated transport was obtained by subtracting the transport velocity in vector-transduced cells from those in OATP1B1 WT or variant-expressing cells. Each point and bar represents the mean ± standard error of the mean from three independent experiments. The solid/dotted lines represent the fitted lines.

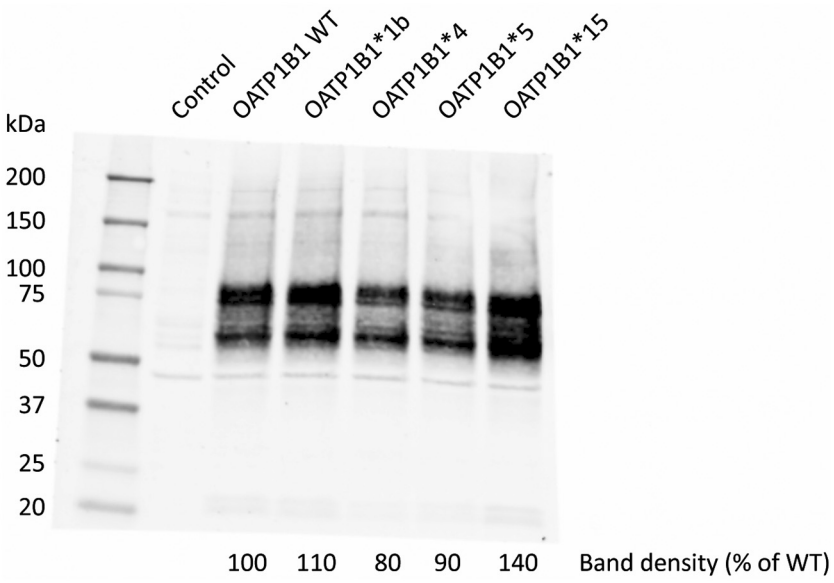

FIG 2 Quantification of OATP1B1 protein expression in HEK293 cells of one of the three independent experiments. Membrane fractions were obtained from HEK293 cells and separated by SDS-PAGE (4% to 20%). The applied amount of protein was 25 μg, and total protein staining (Ponceau) confirmed equal loading across the lanes. The OATP1B1 proteins were detected using a polyclonal anti-OATP2 antibody for OATP1B1 followed by an Alexa Fluor 680 goat anti-rabbit IgG antibody secondary antibody.

and *15 (residual activity, 58%) compared to WT. This is in line with the reduction we observed in transport of the model substrate $E_2$17βG by OATP1B1*5 (residual activity, 44%; Fig. S1), as well as with previously reported residual transport of $E_2$17βG, estrone-3-sulfate, pravastatin, atorvastatin, and rosuvastatin by OATP1B1*5 and *15 (Table 1). Therefore, we hypothesize that the nucleotide change 521T>C is the SNP causing functional alteration of OATP1B1*15 in *in vitro* studies, including our study. However, *in vivo*, no association has been found between rifampicin plasma concentrations and OATP1B1*5 (15–17). For *15, no specific rifampicin exposure data have been reported in literature, even though an increased susceptibility to DILI has been described. We hypothesize that *in vivo*, other uptake transporters such as OATP1B3 may compensate for any reduced activity of OATP1B1*5 and *15 (23). Indeed, Vavricka et al. showed that rifampicin is transported by OATP1B3 and that the apparent K_m value of rifampicin for OATP1B3 (2.3 μM) is slightly lower than for OATP1B1 (13 μM) (24). Furthermore, rifampicin is known for its (auto)inducing effect on metabolizing enzymes and drug transporters, including OATP1B1, probably inducing its net activity. Only limited data are available about whether SNPs impact the extent of OATP1B1 induction (25). Though we expect the impact of OATP1B1 SNPs on intrinsic transport activity and, consequently, rifampicin plasma exposure to be minor, it may still be a contributing factor to the high interindividual variability (up to 5-fold) in rifampicin plasma exposure observed in humans. This may also be relevant to the study and implementation of high-dose rifampicin, where the high interindividual variability can still result in relatively low individual exposures, causing treatment failures and preventing treatment shortening (26). Finally, we acknowledge that the applied overexpression system has its limitations, as it only considers differences in intrinsic activity between polymorphisms in OATP1B1, not including the impact of other transporters and metabolizing enzymes involved in rifampicin distribution and metabolism, and it cannot reflect possible SNP-associated protein expression differences *in vivo*.

In conclusion, we only found a reduction in the *in vitro* intrinsic clearance of rifampicin by OATP1B1*5 and *15. However, we do not expect these reductions to have significant clinical implications, as relevant compensatory mechanisms (e.g., OATP1B3 transport) could easily outweigh these effects *in vivo*.

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 0.2 MB.

ACKNOWLEDGMENTS

We thank H. Kidron (University of Helsinki, Helsinki, Finland) for kindly providing the OATP1B1*5 vector. We thank B. Stieger (University Hospital Zurich, Zurich, Switzerland) for providing the rabbit polyclonal anti-OATP2 antibody.

This project was supported by a Radboudumc RIHS Junior Researcher Round Grant 2017.

J.J.M.W.V.D.H. and J.B.K. are founders of PharmTox (Nijmegen, the Netherlands).

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