British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2017) **83** 1862–1864 1862

# LETTER TO THE EDITOR

# Mechanisms of drug–drug interaction between rifampicin and fusidic acid

**Correspondence** Dr Sylvain Goutelle, Service Pharmaceutique, Hôpital Gériatrique Pierre Garraud, Hospices Civils de Lyon, 136 rue du Commandant Charcot, 69322 Lyon Cedex 05, France. Tel.: +33 (0)4 7216 8099; Fax: +33 (0)4 7216 8102; E-mail: sylvain.goutelle@chu-lyon.fr

**Received** 20 January 2017; **Revised** 15 February 2017; **Accepted** 21 February 2017

Florianne Bel[1], Laurent Bourguignon[1,2,3], Michel Tod[1,2], Tristan Ferry[4,5,6] and Sylvain Goutelle[1,2,3]

*[1]Hospices Civils de Lyon, Groupement Hospitalier Nord, Service Pharmaceutique, Lyon, France, [2]ISPB – Faculté de Pharmacie de Lyon, Université Lyon 1, Lyon, France, [3]UMR CNRS 5558, Laboratoire de Biométrie et Biologie Evolutive, Université Lyon 1, Villeurbanne, France, [4]Department of Infectious Diseases, Hospices Civils de Lyon, Lyon, France, [5]Claude Bernard Lyon 1 University, Lyon, France, and [6]International Centre for Research in Infectiology, CIRI, INSERM U1111, CNRS UMR5308, ENS de Lyon, UCBL1, Lyon, France*

## Tables of Links

| TARGETS |
|---|
| **Transporters** [2] |
| OATP1B1 |
| **Enzymes** [3] |
| CYP3A4 |

| LIGANDS |
|---|
| Rifampicin |

These Tables list key protein targets and ligands in this article which are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [1], and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 [2, 3].

We have read with interest the article published by Marsot *et al.* [4] describing the development of a population pharmacokinetic model of rifampicin (RIF) in patients with osteoarticular infections. The authors have identified a drug–drug interaction (DDI) between rifampicin and fusidic acid (FA), the latter decreasing both RIF clearance and volume of distribution. The authors suggest that this interaction would be due to inhibition of cytochrome P450 3A4 (CYP3A4) by FA. However, there is little information supporting this assumption in the paper.

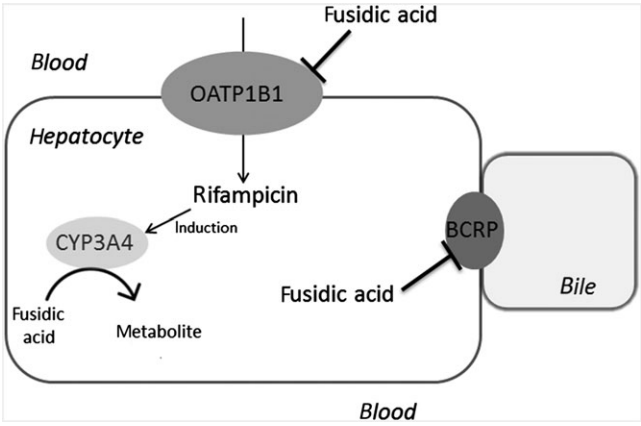
We would like to discuss further the mechanism of this interaction and suggest an alternative hypothesis.

First, it has been shown that RIF is mainly metabolized in the liver into a 25-deacetyl form by esterases (human arylacetamide deacetylase) [5]. RIF is also converted into 3-formylrifampicin by non-enzymatic hydrolysis [6, 7] and it is excreted partially unchanged in the bile and urine. While RIF is a well-known potent CYP3A4 inducer, it does not appear to be a significant substrate of this enzyme. So, FA-induced inhibition of CYP3A4 is unlikely to be the major mechanism of the DDI between RIF and FA.

It has been shown that RIF is a sensitive substrate of the organic anion transporting polypeptide (OATP) 1B1 [8]. This outward transporter [previously known as OATP2, OATP-C and liver-specific organic anion transporter (LST-1) [9, 10]] is expressed on the sinusoidal membrane of hepatocytes and is responsible for the uptake of drugs into the liver [10]. Of note, RIF is also an inhibitor of this transporter [11].

In regard to RIF, two polymorphisms (rs4149032 and rs11045819) of the solute carrier organic anion transporter family member 1B1 (*SLCO1B1*) gene, which encodes OATP1B1, have been associated with reduced RIF exposure due to decreased bioavailability [12, 13], which confirms the clinically significant influence of this transporter on RIF disposition.

DOI:10.1111/bcp.13277




## Figure 1

Proposed mechanisms for the drug–drug interaction between rifampicin and fusidic acid. BCRP, breast cancer resistance protein; CYP3A4, cytochrome P450 3A4; OATP1B1, organic anion transporting polypeptide 1B1

Recently, Gupta *et al*. [14] have studied the inhibition potency of FA towards various metabolic and transporter pathways involved in statin pharmacokinetics. They elegantly showed that FA inhibits OATP1B1, as well as breast cancer resistance protein (BCRP) and CYP3A4. This may explain well the known interaction between FA and statins which may result in overexposure to statins and rhabdomyolysis. They also showed that FA is eliminated primarily by CYP3A4.

To summarize, as RIF is a sensitive substrate of OATP1B1 [15] and FA is an inhibitor of this transporter, we assume that FA could reduce the hepatic uptake and presystemic clearance of RIF, resulting in increased bioavailability and plasma concentrations, as found by Marsot *et al*. [4]. As FA also inhibits BCRP, a reduction in RIF biliary excretion may also participate in the interaction, but this remains to be proven.

Finally, it should be noted that a mutual interaction exists between RIF and FA, as RIF can induce the CYP3A4-mediated metabolism of FA and lower FA concentrations [16].

To conclude, a complex mutual interaction appears to exist between RIF and FA, as summarized in Figure 1. On the one hand, FA can increase the RIF concentration. On the other hand, RIF can decrease the FA concentration. As RIF also induces its own metabolism, the time course, as well as the clinical consequences, of this mutual interaction are difficult to predict in individual patients, although the association has been associated with a favourable outcome in patients with methicillin-resistant *Staphylococcus aureus* implant-associated bone and joint infection [17]. Therapeutic drug monitoring of both agents may be of interest for the clinical management of this interaction.

## Competing Interests

There are no competing interests to declare.

## References


**1** Southan C, Sharman JL, Benson HE, Faccenda E, Pawson AJ, Alexander SP, *et al*. The IUPHAR/BPS guide to PHARMACOLOGY in 2016: towards curated quantitative interactions between 1300 protein targets and 6000 ligands. Nucl Acids Res 2016; 44 (Database Issue): D1054–68.

**2** Alexander SPH, Kelly E, Marrion N, Peters JA, Benson HE, Faccenda E, *et al*. The concise guide to PHARMACOLOGY 2015/16: Transporters. Br J Pharmacol 2015; 172: 6110–202.

**3** Alexander SPH, Fabbro D, Kelly E, Marrion N, Peters JA, Benson HE, *et al*. The concise guide to PHARMACOLOGY 2015/16: Enzymes. Br J Pharmacol 2015; 172: 6024–109.

**4** Marsot A, Ménard A, Dupouey J, Muziotti C, Guilhaumou R, Blin O. Population pharmacokinetics of rifampicin in adult patients with osteoarticular infections: interaction with fusidic acid. Br J Clin Pharmacol 2017; 83: 1039–47.

**5** Nakajima A, Fukami T, Kobayashi Y, Watanabe A, Nakajima M, Yokoi T. Human arylacetamide deacetylase is responsible for deacetylation of rifamycins: rifampicin, rifabutin, and rifapentine. Biochem Pharmacol 2011; 82: 1747–56.

**6** Loos U, Musch E, Jensen JC, Mikus G, Schwabe HK, Eichelbaum M. Pharmacokinetics of oral and intravenous rifampicin during chronic administration. Klin Wochenschr 1985; 63: 1205–11.

**7** Reith K, Keung A, Toren PC, Cheng L, Eller MG, Weir SJ. Disposition and metabolism of14C-rifapentine in healthy volunteers. Drug Metab Dispos 1998; 26: 732–8.

**8** Tirona RG, Leake BF, Wolkoff AW, Kim RB. Human organic anion transporting polypeptide-C (SLC21A6) is a major determinant of rifampin-mediated Pregnane X receptor activation. J Pharmacol Exp Ther 2003; 304: 223–8.

**9** Shitara Y, Maeda K, Ikejiri K, Yoshida K, Horie T, Sugiyama Y. Clinical significance of organic anion transporting polypeptides (OATPs) in drug disposition: their roles in hepatic clearance and intestinal absorption. Biopharm Drug Dispos 2013; 34: 45–78.

**10** Kalliokoski A, Niemi M. Impact of OATP transporters on pharmacokinetics. Br J Pharmacol 2009; 158: 693–705.

**11** Vavricka SR, Van Montfoort J, Ha HR, Meier PJ, Fattinger K. Interactions of rifamycin SV and rifampicin with organic anion uptake systems of human liver. Hepatology 2002; 36: 164–72.

**12** Chigutsa E, Visser ME, Swart EC, Denti P, Pushpakom S, Egan D, *et al*. The SLCO1B1 rs4149032 polymorphism is highly prevalent in south Africans and is associated with reduced rifampin concentrations: dosing implications. Antimicrob Agents Chemother 2011; 55: 4122–7.

**13** Weiner M, Peloquin C, Burman W, Luo C-C, Engle M, Prihoda TJ, *et al*. Effects of tuberculosis, race, and human gene *SLCO1B1* polymorphisms on rifampin concentrations. Antimicrob Agents Chemother 2010; 54: 4192–200.

**14** Gupta A, Harris JJ, Lin J, Bulgarelli JP, Birmingham BK, Grimm SW. Fusidic acid inhibits hepatic transporters and metabolic enzymes: potential cause of clinical drug–drug interaction observed with statin coadministration. Antimicrob Agents Chemother 2016; 60: 5986–94.

**15** Elsby R, Hilgendorf C, Fenner K. Understanding the critical disposition pathways of statins to assess drug–drug interaction risk during drug development: it's not just about OATP1B1. Clin Pharmacol Ther 2012; 92: 584–98.

**16** Pushkin R, Iglesias-Ussel MD, Keedy K, MacLauchlin C, Mould DR, Berkowitz R, *et al*. A randomized study evaluating oral fusidic acid (CEM-102) in combination with oral rifampin compared with standard-of-care antibiotics for treatment of prosthetic joint infections: a newly identified drug–drug interaction. Clin Infect Dis Off Publ Infect Dis Soc Am 2016; 63: 1599–604.

**17** Ferry T, Uçkay I, Vaudaux P, François P, Schrenzel J, Harbarth S, *et al*. Risk factors for treatment failure in orthopedic device-related methicillin-resistant *Staphylococcus aureus* infection. Eur J Clin Microbiol Infect Dis Off Publ Eur Soc Clin Microbiol 2010; 29: 171–80.