

COMMENTARY

Commentary on: “Influence of OATP1B1 Function on the Disposition of Sorafenib- β -D-Glucuronide”

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INTRODUCTION

Approaches to predict and characterize drug–drug interactions (DDI) mediated by a single drug-metabolizing enzyme or a single transporter are well established. However, complex DDIs, where multiple metabolic and transport processes are involved, require an integrative translational approach.^{1,2} If a drug undergoes reversible metabolism, the net contribution of the processes of metabolism, uptake, and/or efflux transport on drug disposition and response is difficult to deconvolute and is particularly important for narrow therapeutic index drugs.

The importance of the interplay between drug transporter(s) and drug metabolizing enzyme(s) on the processes of drug absorption, distribution, and metabolism was realized over 20 years ago.³ Since then, numerous investigations have elucidated the impact of transporter-mediated tissue distribution on metabolite formation and its consequential effect on drug safety and efficacy. Recent studies, fueled by the knowledge of the role transporters play in DDIs, have enhanced our understanding of the clinical significance of transporter–metabolism interplay, where the metabolites themselves are victims and perpetrators of transporter-mediated DDIs. An excellent example of this is highlighted in the article “Influence of OATP1B1 function on the disposition of sorafenib- β -D-glucuronide” by Bins *et al.*⁴ This eloquent bench-to-bedside investigation builds upon previous mechanistic studies⁵ by evaluating the clinical significance of inhibiting OATP1B1-mediated transport of the glucuronide metabolite of sorafenib, sorafenib- β -D-glucuronide (SG). This study is particularly unique, since SG demonstrates a novel and circuitous route of elimination called “hepatocyte-hopping,” whereby after SG formation in the hepatocyte, SG can undergo sinusoidal efflux *via* ABCC3 and is actively taken up by neighboring hepatocytes *via* OATP1B1/OATP1B3.⁶ In Bins *et al.*, through the use of *in vitro* transporter assays and mouse models, the authors demonstrate that SG is a substrate of mouse Oatp1b2 and human OATP1B1, and its uptake into liver cells is inhibited by rifampin, resulting in enhanced SG concentrations in plasma and a 90% reduction of the liver-to-plasma ratio of SG in mice. In addition, in a clinical DDI study evaluating the concomitant administration of sorafenib with rifampin in cancer

patients, the hepatocyte-hopping hypothesis of SG is supported, as plasma concentrations of SG are indeed increased in cancer patients treated with the combination of sorafenib and rifampin vs. sorafenib alone.

Sorafenib is a nonspecific kinase inhibitor approved for the treatment of hepatocellular, renal cell, and thyroid carcinomas.⁷ Sorafenib displays high interpatient pharmacokinetic (PK) variability⁸ that is not explained by patient demographics, organ function, or genetic variants of CYP3A and UGT1A9.⁹ This interpatient PK variability has clinical consequences, as >40% of the patient population experience toxicities that require a dose reduction and the patients who experience a grade ≥ 3 toxicity from sorafenib treatment also have higher sorafenib exposure.⁸ In addition to the PK variability of sorafenib, plasma exposures of sorafenib appear to decrease with time.⁸ While the mechanism for this observation is not known, there may be direct clinical consequences for reduced exposures, as patients with lower sorafenib exposure have poorer treatment outcomes compared to patients with higher sorafenib exposures.¹⁰

In addition to sinusoidal efflux, SG in the liver can also be secreted into the bile *via* ABCC2, deconjugated by bacteria to parent sorafenib, and then reabsorbed into the systemic circulation from the intestine.⁶ In Bins *et al.*, despite the observed increase in SG plasma concentrations and the potential for SG eliminated into the bile to undergo hydrolysis to sorafenib, plasma levels of sorafenib are unchanged with rifampin coadministration. Therefore, the clinical relevance of this observed DDI between rifampin and SG may be limited. However, with the potential that systemic accumulation of SG may contribute to the observed safety events of sorafenib, additional research may be warranted in order to guide the use of OATP1B inhibitors in cancer patients treated with sorafenib, as well as with other kinase inhibitors that undergo glucuronidation, such as dasatanib, regorafenib, and trametinib, as noted by Bins *et al.*

The ability to define the relationship between drug disposition/response and drivers of variability is at the center of precision medicine and translational science efforts. Impactful problem solving is dependent on prior observations and challenging previous assumptions with the combination of novel preclinical models and clinical experimental approaches, which may provide unambiguous results. In the publication

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by Bins *et al.*, the significance of drug transport as a determinant of a DDI where the victim substrate is the conjugate SG highlights the potential significance of rifampin-mediated OATP1B inhibition. It is curious to speculate that because liver is both the target and the major organ of sorafenib disposition, altered SG clearance *via* hepatocyte hopping may influence sorafenib's target access and therapeutic index. Finally, commonly administered concomitant drugs (e.g., statins and glibenclamide), complementary alternative medicines (e.g., curcumin, St. John's wort), and endogenous substrates may differentially impact sorafenib and SG disposition and response. The findings described in Bins *et al.* may have broader application to various drugs with major glucuronide metabolites exhibiting a narrow therapeutic index. Defining these intertwined processes is a tremendous opportunity for clinical and translational scientists to explore, particularly in determining whether these findings are broadly applicable to other drugs. Through understanding the dual role of complex DDIs and patient-specific covariates (e.g., genetics, comorbidities) on drug response, individualized therapy to maximize therapeutic benefit can be achieved.

Conflict of Interest. J.A.W. and K.M.M. are paid employees of Genentech, a subsidiary of Roche. L.Z.B. declared no conflict of interest.

1. Wienkers, L.C. & Heath, T.G. Predicting in vivo drug interactions from in vitro drug discovery data. *Nat. Rev. Drug Discov.* **10**, 825–833 (2005).

2. Kusuhara, H. & Sugiyama, Y. Pharmacokinetic modeling of the hepatobiliary transport mediated by cooperation of uptake and efflux transporters. *Drug Metab. Rev.* **3**, 539–550 (2010).
3. Wachter, V.J., Wu, C.Y. & Benet, L.Z. Overlapping substrate specificities and tissue distribution of cytochrome P450 3A and P-glycoprotein: implications for drug delivery and activity in cancer chemotherapy. *Mol. Carcinog.* **3**, 129–134 (1995).
4. Bins S., *et al.* Influence of OATP1B1 function on the disposition of sorafenib- β -D-glucuronide. *Clin. Transl. Sci.* (2017). <https://doi.org/10.1111/cts.12458>
5. Jusuf, D., van de Steeg, E. & Schinkel, A.H. Hepatocyte hopping of OATP1B substrates contributes to efficient hepatic detoxification. *Clin. Pharmacol. Ther.* **5**, 559–562 (2012).
6. Vasilyeva, A., *et al.* Hepatocellular shuttling and recirculation of sorafenib-glucuronide is dependent on Abcc2, Abcc3, and Oatp1a/1b. *Cancer Res.* **13**, 2729–2736 (2015).
7. NEXAVAR (sorafenib) [package insert]. Bayer HealthCare Pharmaceuticals Inc., Wayne, NJ; October 2010.
8. Boudou-Rouquette, P., *et al.* Variability of sorafenib toxicity and exposure over time: a pharmacokinetic/pharmacodynamic analysis. *Oncologist* **9**, 1204–1212 (2012).
9. Jain, L., *et al.* Population pharmacokinetic analysis of sorafenib in patients with solid tumours. *Br. J. Clin. Pharmacol.* **2**, 294–305 (2011).
10. Pécuchet, N., *et al.* Sorafenib in advanced melanoma: a critical role for pharmacokinetics? *Br J Cancer.* **107**(3), 455–461 (2012).

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