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Intestinal P-gp and Putative Hepatic OATP1B Induction: ITC Perspective on Drug Development Implications

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Abstract

There is an increasing interest in transporter induction (i.e., decreased systemic drug exposure due to increased efflux-limited absorption or transporter-mediated clearance) as a mechanism of drug-drug interactions (DDIs), although evidence of clinical relevance is still evolving. Intestinal P-glycoprotein (P-gp) and hepatic organic anion transporting polypeptides 1B (OATP1B) can be important determinants of drug absorption and disposition, as well as targets for DDIs. Current data indicate that intestinal P-gp protein levels can be induced ≤3-4 fold in humans primarily with pregnane X receptor (PXR) activators, and that this induction can decrease the systemic exposure of drugs with P-gp efflux-limited absorption (e.g., ≤67% decrease in the exposure of total dabigatran following rifampin multiple oral dosing). Evaluation of the clinical relevance of P-gp induction as a DDI mechanism must consider the induction potential of the perpetrator drug for P-gp and attenuation of exposure of the victim drug in the context of its therapeutic window. Practical drug development recommendations are provided herein. Reports are contradictory on OATP1B induction by PXR activators in human hepatocytes and liver biopsies. Some clinical investigations demonstrated that rifampin pretreatment decreased exposure of OATP1B substrates, while other studies found no differences, and the potential involvement of other mechanisms in these observed DDIs cannot be definitively ruled out. Thus, further studies are needed to understand hepatic OATP1B induction and potential involvement of other mechanisms contributing to reduced exposure of OATP1B substrates. This review critically summarizes the state-of-the-art on intestinal P-gp and hepatic OATP1B induction, and highlights implications for drug development.

Whitepaper

During drug development, transporter-related drug-drug interaction (DDI) assessment has traditionally focused on inhibition eliciting increased drug exposure and potential safety issues. Induction is a well-established and important mechanism of DDIs for key cytochrome P450 (CYP) enzymes, which can result in decreased drug exposure and efficacy. In principle, transporter induction could similarly result in diminished drug concentrations and efficacy due to attenuated absorption or enhanced clearance. To-date, regulators have acknowledged transporter induction as a DDI mechanism of potential clinical relevance, specifically for P-glycoprotein (P-gp), but advise case-by-case consultation on clinical evaluation and recognize the lack of predictive in vitro assays (FDA Clinical DDI Guidance, 2017, https://www.fda.gov/media/82734/download; FDA In Vitro DDI Guidance, 2020, https://www.fda.gov/media/134582/download). Emerging research in the area of drug transporter induction raises questions regarding whether this mechanism merits consideration as a DDI mechanism, and if so, what would be the practical strategies to evaluate such DDIs during drug development.

Unlike CYP enzyme induction, accurate interpretation of clinical DDI data regarding apparent transporter induction may be confounded by the lack of specific transporter probe substrates and the limited ability to obtain relevant tissues in humans to quantify the change in protein levels. The decrease in exposure attributed to induction of one transporter may be confounded by the modulation of other drug absorption and/or clearance mechanisms (e.g., metabolism and/or alternate transport pathways). Beyond traditional induction (increased mRNA and/or protein levels), increased transporter activity has also been postulated to occur via enhanced plasma membrane trafficking, allosteric-type activation, increased protein stabilization, or decreased degradation (1); however, the clinical relevance of enhanced transporter function via these mechanisms is presently unclear and therefore beyond the scope of this mini-review.

Induction of several transporters, defined as increased mRNA and/or protein expression, has been reported based on human biopsy and/or in vitro data (e.g., multidrug resistance proteins 2 and 3, organic solute transporters α/β, and P-gp (2–4)); however, our in vivo understanding of transporter induction as a clinically-relevant DDI mechanism is still evolving. Examination of clinical reports supporting transporter induction to elicit decreased exposure of substrate drugs flagged only intestinal P-gp and hepatic organic anion transporting polypeptides 1B (OATP1B). Evidence summarized in the following section supports intestinal P-gp induction as a DDI mechanism. However, as detailed below, it remains unclear whether hepatic OATP1B are inducible due to conflicting non-clinical and clinical data. Consensus expert opinions on drug development implications for these apparent changes are discussed.

Intestinal P-glycoprotein (P-gp)

P-gp is an efflux transporter, which can attenuate intestinal absorption, restrict blood-brain barrier penetration, as well as mediate biliary and urinary secretion of substrate drugs. Clinically-relevant DDIs via induction of intestinal P-gp have been reported (5, 6). Despite suggestions by some in vitro studies, clinical relevance is lacking for DDIs due to induction of P-gp expressed in the blood-brain barrier (directly demonstrated in clinical brain imaging studies), liver and kidney (no evidence for decreased half-life of metabolically-stable substrates; Tables 1–2) (2, 7).

Induction of intestinal P-gp has been established by up to a ~3-4-fold increased protein expression in human intestinal biopsies [(5, 6); more recent quantitative proteomics indicated a ~2-fold increase (8)], as well as functionally by decreased oral bioavailability of the P-gp substrates digoxin and talinolol following multiple-dose treatment with pregnane X receptor (PXR) activators, such as rifampin or St. John’s Wort (Table 1). Dabigatran etexilate, a prodrug considered a relatively specific intestinal P-gp substrate (9), exhibited up to 67% decrease in total dabigatran exposure (parent plus glucuronides) after a 10-day treatment with 10 to 600 mg rifampin (10). Carbamazepine and rifabutin, clinically weaker clinical PXR inducers (8), elicited lower changes in total dabigatran exposure (11) (Table 1). In the case of P-gp-substrate prodrugs (e.g., sofosbuvir, tenofovir alafenamide), transporter induction is expected to increase intestinal residence time, which would enhance prodrug hydrolysis and result in decreased systemic prodrug exposure, with no impact on elimination

half-life. Decreased maximal concentration (Cmax) and area under the concentration-time curve (AUC) of sofosbuvir and tenofovir alafenamide, with unaltered half-life, were observed following pretreatment with multiple-dose rifampin (Table 2).

In addition to decreased systemic exposure (i.e., effect on Cmax and AUC), intestinal P-gp induction is expected to attenuate both the fraction absorbed and absorption rate (i.e., delayed time of Cmax (Tmax) and decreased absorption rate reflected in decreased Cmax). For metabolically-stable drugs with quantifiable renal clearance (e.g., digoxin), urinary parent drug recovery can be used as a surrogate for decrease in the fraction absorbed; however, caution is warranted when the P-gp-substrate also is metabolized by CYP3A, whose induction alone may decrease parent drug recovery in urine. Clinical studies conducted to-date (Tables 1–2) provide limited direct support for delayed Tmax due to high inter-individual variability [e.g., digoxin and talinolol Tmax values were significantly 24-35% longer following multiple-dose rifampin (5, 6)]. Future studies aiming to demonstrate delayed absorption rate due to intestinal P-gp induction should ensure adequately intensive pharmacokinetic sampling during the absorption phase, as well as report individual absorption changes in addition to mean data.

Evaluation of P-gp Induction: Perpetrator DDI Potential

Clinically, intestinal P-gp induction has been observed primarily with PXR activators (5, 8, 10, 11). In vitro studies demonstrated that activation of vitamin D receptor and the constitutive androstane receptor also may contribute to the induction of intestinal P-gp, although clinical relevance is presently unknown (12, 13). The first step in assessing clinical relevance of PXR activation is by comparison of the PXR EC_{50} to the intestinal drug concentration estimated as the highest clinical dose/250 mL (FDA, 2020). Further, induction of intestinal P-gp via PXR as a likely DDI concern could be considered for clinically-relevant CYP3A inducers. This approach is analogous to the assessment of CYP2C induction, which is studied only for clinically-relevant CYP3A inducers, since CYP3A induction is the most sensitive and exhibits the greatest induction magnitude by PXR activation (FDA, 2020).

Evaluation of the clinical relevance of P-gp induction as a DDI mechanism must consider the induction potential of the P-gp perpetrator that may attenuate exposure of the victim drug in the context of its therapeutic window. Intestinal P-gp induction is functionally lesser in magnitude than combined hepatic and intestinal CYP3A induction effect (10, 11). Specifically, a strong CYP3A inducer like rifampin reduces AUC of a sensitive CYP3A substrate like midazolam by >80% (“strong induction” defined as exposure ratio <0.2), but elicits at most a 67% decrease in total dabigatran (“moderate induction” defined as exposure ratio 0.2 to 0.5) (Table 1) (10, 11). Therefore, a clinical intestinal P-gp induction study may be warranted for investigational drugs that are strong CYP3A inducers when dosed with P-gp substrates whose efficacy may be impaired by ≤67% exposure reductions (e.g., digoxin).

Weak clinical CYP3A inducers (midazolam exposure ratio 0.8-0.5) are not expected to elicit clinically-relevant intestinal P-gp induction (total dabigatran exposure ratio 0.8-1.25) (10, 11). Less clinical data is available on the induction effect of moderate CYP3A inducers (e.g., efavirenz) on P-gp substrates. Assuming a less pronounced induction effect on P-gp by a

moderate CYP3A inducer (10, 11), a clinical study may be considered for co-medications that are substrates of P-gp (and also other transporters/enzymes inducible via PXR) if efficacy may be impaired by exposure reductions ≤50%. Notably, rifampin had larger induction effects on some P-gp substrates than its effect on dabigatran (Tables 1–2), a relatively specific intestinal P-gp substrate (9). It is speculated that induction of other mechanisms may also contribute to the overall effect: e.g., velpatasvir (also substrate of CYP3A, CYP2B6, CYP2C8, BCRP), glecaprevir and voxilaprevir (also substrates of CYP3A, OATP1B, BCRP), pibrentasvir and sofosbuvir (also substrates of BCRP) (Table 2). Thus, the effect of a moderate CYP3A inducer on such drugs may be larger than anticipated with P-gp induction alone and may warrant evaluation if efficacy of such drugs is sensitive to moderate decreases in exposure.

Evaluation of P-gp Induction: Victim DDI Potential

Intestinal P-gp induction may pose a victim DDI risk for investigational drugs that are P-gp substrates and exhibit efflux-limited absorption. Note that many drugs with P-gp-limited absorption are also appreciably (>25%) cleared by CYP3A; therefore, in many cases the intestinal P-gp induction victim DDI risk is evaluated as part of the CYP3A clinical induction study. Otherwise for investigational drugs not cleared by CYP3A, whose intestinal absorption is P-gp-limited and efficacy will be impaired by exposure reductions ≤67%, a clinical DDI study with multiple oral dosing of a prototypical PXR inducer (e.g., rifampin) or a relevant inducer co-medication should be considered. As rifampin also is an inhibitor of intestinal P-gp and BCRP, induction studies should be designed with staggered dosing of rifampin and the investigational drug (e.g., last rifampin dose administered 12 hours before investigational drug) (14).

Evaluation of P-gp Induction: DDI Prediction Approaches

For evaluating an investigational drug as a putative clinical P-gp inducer, Lutz and colleagues have proposed a calibration approach to predict PXR-mediated intestinal P-gp induction magnitude based on studies with rifabutin, carbamazepine, and a range of rifampin doses that quantified decreases in exposure of CYP3A (midazolam), P-gp (dabigatran etexilate), and several other CYP and transporter probes (10, 11). These data were used to establish a quantitative relationship between intestinal P-gp induction (total dabigatran exposure ratio) and overall hepatic/intestinal CYP3A induction (midazolam exposure ratio). For investigational drugs that are known PXR activators in vitro and show clinically-relevant in vitro induction of CYP3A, a multiple-dose DDI study with midazolam as a probe will most likely be conducted during drug development. Based on the observed midazolam exposure ratio, the exposure ratio of total dabigatran can be estimated from the established quantitative relationship to determine whether the investigational drug is a putative clinical P-gp inducer (10, 11). Notably, for victim DDI assessment, the in vivo induction calibration approach has limited utility when the investigational drug is substantially metabolized by inducible CYP enzymes (e.g., extensive overlap exists between P-gp and CYP3A substrates).

Physiologically-based pharmacokinetic (PBPK) modeling and simulation is now a widely-adopted strategy for the evaluation of DDI risks. A PBPK model of digoxin that

incorporated a 3.5-fold induction of intestinal P-gp by multiple-dose rifampin accurately described the observed decrease in oral digoxin exposure (15). Notably, this PBPK model incorporated information from intestinal P-gp protein quantification in biopsies obtained from the same digoxin study subjects (5). Subsequent PBPK modeling of the effects of multiple high-dose rifampin on digoxin, talinolol, and dabigatran etexilate (Table 1) estimated maximal induction of intestinal P-gp within this ~3-4-fold range (5, 6, 16). Therefore, it was reasonably assumed that clinical induction of intestinal P-gp by multiple high-dose rifampin represents maximal induction response (strongest clinical PXR activator). Therefore, PBPK modeling could be used to interrogate whether a ~3-4-fold induction of intestinal P-gp impacts the absorption and exposure of likely co-medications that are P-gp substrates or an investigational drug with P-gp-limited absorption (15).

For perpetrator DDI assessment, the in vivo induction calibration proposed by Lutz and colleagues (10, 11) may provide an estimate of the magnitude of intestinal P-gp induction that can inform further PBPK modeling. However, the utility of this in vivo induction calibration is currently limited to rare instances of investigational drugs that are cleared by otherwise uninducible pathways (e.g., urinary excretion via glomerular filtration). A validated in vitro system to study intestinal P-gp induction currently is not available and quantitative approach to predict the exposure of inducer drugs in the gut is still limited. Therefore, for foreseeable future determining definitively whether a drug induces intestinal P-gp and subsequent dosing recommendation will be based on clinical studies in conjunction with PBPK modeling and/or clinical induction calibration approaches.

P-gp Induction: Knowledge Gaps and Future Directions

Induction potential of P-gp along the human intestine is not fully characterized. P-gp protein levels increase from the duodenum to jejunum/ileum approximately 3-fold, and decrease in the lower small intestine and colon. However, induction of P-gp protein expression has only been studied in duodenal biopsies (5, 6), and functionally examined with immediate release formulations, whose absorption largely occurs in the jejunum (Table 1–2). Available clinical studies with immediate release formulations of P-gp substrates, and their PBPK modeling, suggest the magnitude of P-gp induction in duodenum is also reflective of the jejunum (15, 16). However, definitive support of P-gp induction in the jejunum will need human biopsy tissues and/or data from an extended release formulation of a P-gp sensitive substrate to facilitate our clinical understanding of potential regional differences in intestinal P-gp induction.

Hepatic Organic Anion Transporting Polypeptide (OATP)1B

Two members of the OATP1B subfamily, OATP1B1 and OATP1B3, are expressed on the basolateral domain of human hepatocytes. OATP1B-mediated uptake can be rate-determining in hepatic drug clearance and its inhibition can result in large increases in systemic drug exposure and safety concerns (e.g., hydrophilic statins). In contrast, clinical evidence for hepatic OATP1B induction is controversial (17). Rifampin is a potent OATP1B inhibitor and single-dose administration is used clinically to assess OATP1B inhibition,

whereas multiple-dose rifampin is used extensively to investigate induction effects mediated by PXR (e.g., CYP3A/midazolam).

Reduced exposure of the OATP1B-substrate statins (e.g., pravastatin and rosuvastatin), as well as the OATP1B endogenous biomarkers (e.g., coproporphyrins I and III), has been reported following multiple- versus single-dose rifampin (Table 3). However, clinical data regarding some of these hepatic OATP1B probes are conflicting. For instance, rosuvastatin exposure was not changed (AUC ratio 0.8-1.25) by multiple administration of 450 mg rifampin (18, NDA 21366); in contrast, a more recent study reported dose-dependent decreases in rosuvastatin and pravastatin exposure after multiple-dose rifampin (2 to 600 mg); the weaker PXR inducer, carbamazepine, also reduced rosuvastatin and pravastatin exposure 61-62% (10, 11). Multiple dosing of 600 mg rifampin increased pitavastatin acid exposure 29% (NDA 22363), although this result may be confounded by rifampin's OATP1B inhibition, whereas the more moderate CYP3A inducer, efavirenz, did not elicit pitavastatin acid exposure ratio <0.8 (19) (Table 3). While multiple administration of 600 mg rifampin reduced plasma coproporphyrin I and III concentrations compared to single-dose rifampin, no change was noted relative to rifampin pre-dose coproporphyrin baselines (20) (Table 3).

Hepatic OATP1B induction as a DDI mechanism has been considered in a PBPK model optimized with observed rifampin multiple dose-dependent decreases in pravastatin exposure (10, 21). This middle-out PBPK approach estimated a 2.3-fold maximal OATP1B induction in human liver by multiple-dose rifampin (21) under the assumption that rifampin OATP1B EC_{50} is the same as that for CYP3A4 (21), although this strategy can be questioned based on currently available in vitro (4) and clinical data for rifampin (Table 3). Incorporation of OATP1B induction into PBPK models for the OATP1B substrates glibenclamide, repaglinide, and coproporphyrin I more accurately described the clinically observed interactions following multiple-dose rifampin administration than models incorporating only CYP induction and OATP1B inhibition (21). Nonetheless, improved PBPK model fit can only support a hypothesis, but does not provide unequivocal mechanistic proof of a DDI mechanism.

As OATP1B-mediated uptake is considered the rate-determining step for hepatic elimination of several metabolically-stable statins and coproporphyrins, it is tempting to attribute this reduced exposure following administration of multiple-dose rifampin to OATP1B induction. However, evidence supporting the OATP1B induction by potent PXR activators (e.g., rifampin) is controversial. For instance, rifampin (600 mg/day for 1 week) did not affect OATP1B mRNA and protein expression in human liver biopsies, consistent with a lack of OATP1B induction via PXR in human and monkey hepatocytes in vitro, as well as in vivo in cynomolgus monkeys using pitavastatin as OATP1B substrate (2, 4). The reports on in vitro induction of OATP1B via PXR activators in different human hepatocyte models are also controversial, ranging from none to weak/moderate induction (0.81 to 2.7 and 0.63 to 5.5 for OATP1B1 and OATP1B3, respectively) (3, 4). Transcriptional regulation of OATP1B is complex, and involves the liver X receptor α, farnesoid X receptor, hepatic nuclear factor 1α and 4α, but not PXR and constitutive androstane receptor, highlighting the need to further understand the clinical relevance of other regulatory pathways beyond PXR (22 and

references therein). Despite growing evidence suggesting that the OATP1B function could also be regulated by post-translational modification potentially via glycosylation, phosphorylation, and ubiquitination, or by alteration of protein degradation, such regulation would result in reduced, rather than increased transport function of OATP1B based on currently available in vitro observations (22). Consequently, these mechanisms are likely not relevant to potential induction of OATP1B activity, but additional data are needed to substantiate this hypothesis.

Interpretation of clinical findings also needs to consider other potential mechanisms that may contribute to the decrease in exposure of OATP1B substrates. For drugs like repaglinide, where all hepatobiliary clearances affect its hepatic disposition, induction of metabolic clearance by multiple-dose rifampin may modify its rate-determining step and drive changes in the systemic exposure that may be incorrectly attributed to OATP1B induction (Table 3). The disposition of rosuvastatin, pravastatin, and pitavastatin involves other transporters (e.g., OATP2B1, BCRP, MRP2), as well as uridine 5-diphosphoglucuronosyl transferases (23), which also may be modulated by the perpetrator (e.g., rifampin), potentially confounding data interpretation (see Table 3 for details). For instance, intestinal and hepatic MRP2 is induced by rifampin (2, 24, 25), which could contribute to reduced pravastatin exposure following multiple-dose rifampin. An additional consideration for interpretation of conflicting OATP1B induction findings is that some PXR agonists (e.g., rifampin) are substrates of OATP1B, and their hepatic concentrations may be higher than non-substrate PXR agonists. Finally, the timing of administration of the inducer versus OATP1B probe is an important consideration; in several cases victim drugs were administered 12-24 h after the last rifampin dose, which would reduce rifampin concentrations available for OATP1B inhibition resulting in cleaner evaluation of potential induction effects (Table 3).

Summary

Present clinical evidence supports intestinal P-gp induction by PXR activators and should be a DDI consideration for development of drugs that are PXR activators and/or exhibit intestinal P-gp efflux-limited absorption (see recommendations in “Intestinal P-gp” section). Further studies are needed to advance the understanding of reduced exposure observed for some OATP1B probes after multiple-dose rifampin and other PXR activators. Delineation of OATP1B induction versus modulation of other potential mechanisms is essential, because hepatic OATP1B induction would have important implications for the efficacy and safety of many drugs. More in-depth knowledge about the impact of inducers on all the transporters/enzymes responsible for probe substrate disposition in humans is needed. Validation of novel tools/approaches in human physiologically-relevant systems to assess the clinical consequences of such complex interactions would be a major advance in the field. Considering the interest in transporter induction, our understanding of clinical relevance of transporter induction as a DDI mechanism will continue to grow.

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Abbreviations:

AUC	area under the concentration-time curve
BCRP	breast cancer resistance protein
CYP	cytochrome P450
DDI	drug-drug interaction
Cmax	maximal concentration
MRP	multidrug resistance associated protein
OATP	organic anion transporting polypeptide
OST	organic solute transporter
P-gp	P-glycoprotein
PBPK	physiologically-based pharmacokinetic
PXR	pregnane X receptor
Tmax	time of Cmax

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Table 1:

Clinical DDIs supporting intestinal P-gp induction.

Inducer (Dose and Pre-treatment Duration)	Substrate (Dose)	Dosing interval between substrate and inducer	No. of subjects	AUC (% ↓)	C_{max} (% ↓)	$t_{1/2}$ (% ↓)
Rifampin (600 mg/d x 10d)	Digoxin (1 mg)	NR	8	30[a]	52	↔
	Digoxin (1 mg IV)			15[a]	↔	↔
Rifampin (600 mg/d x 10d)	Digoxin (1 mg IV)	Staggered (~12 h)	8	27[a]	19	↔
Rifampin (600 mg/d x 14d)	Digoxin (0.5 mg)	Staggered (~12 h)	16	19[a,b]	↔	NR
Rifampin (600 mg/d x 15d)		Concomitant	9	25↑[a,b]	55↑[b]	NR
Rifampin (300 mg twice daily x 6d)	Digoxin (0.4 mg)	NR	16	16[a]	23	↔
Rifampin (300 mg twice daily x 6d)	Digoxin (0.25 mg)	Staggered (NR)	18	25	38	↔
St John's wort LI160 (300 mg extract three times daily x 13d)	Digoxin (0.25 mg)	NR	18	23[a]	36	↔
St John's wort LI160 (300 mg dried hypericum extract three times daily)	Digoxin (0.25 mg/d x 10d with placebo or St John's wort)	Concomitant	13	25[a]	26	↔
St John's wort LI160 (300 mg dried hypericum extract three times daily)	Digoxin (0.2–0.3 mg/d x 14d with placebo or St John's wort)	Digoxin (30 min before St John's wort)	6	25[a]	37	↔
St John's wort (300 mg three times daily x 14d)	Digoxin (0.5 mg)	Staggered (NR)	8	18[a]	NR	NR
St. John's wort (Esbericum, 120 mg twice daily)	Digoxin (0.25 mg/d x 10d with placebo or St John's wort)	NR	16	↔	↔	NR
Rifampin (2 mg mg/d x 10d)	Dabigatran etexilate (75 mg)	Staggered (~12 h)	20	19 ↑	↔	↔*
Rifampin (10 mg/d x 10d)				41[b]	43[b]	↔*
Rifampin (75 mg/d x 10d)				62[b]	62[b]	↔*
Rifampin (600 mg/d x 10d)				67[b]	69[b]	↔*
Rifampin (600 mg/d x 7d)	Dabigatran etexilate (150 mg)	Staggered (12 h)	24	67[b]	65[b]	↔
Carbamazepine (300 mg twice daily x 10d)	Dabigatran etexilate (75 mg)	Staggered (~12 h)	24	29[b]	33[b]	↔*
Rifabutin (300 mg/d x 11d)	Dabigatran etexilate (75 mg)	Staggered (~12 h)	20	19[b]	13[b]	↔*

Inducer (Dose and Pre-treatment Duration)	Substrate (Dose)	Dosing interval between substrate and inducer	No. of subjects	AUC (% ↓)	C_{max} (% ↓)	$t_{1/2}$ (% ↓)
Rifampin (600 mg/d)	Talinolol (100 mg/d x 7d alone or 6d with rifampin)	Staggered (~13 h)	8	35	38	15
	Talinolol (30 mg IV after 9d rifampin)	Staggered (NR)		21	19	11
Carbamazepine (600 mg once daily)	Talinolol (100 mg/d x 5d alone or x 13d with carbamazepine)	Staggered (~12 h)	7	15[a]	NR	↔
	Talinolol (30 mg IV after 17d carbamazepine)			↔	NR	↔
St John's wort LI160 (300 mg Jarsin 300® three times daily x 12d)	Talinolol (50 mg)	Staggered (NR)	9	31	↔	↔
	Talinolol (30 mg IV)			↔	NR	↔
Quercetin (500 mg/d x 13d)	Talinolol (100 mg)	Staggered (NR)	18	20	24	↔

All data were obtained from University of Washington Drug Interaction Solutions database, product prescribing information, and Drugs@FDA Clinical Pharmacology reviews.

Notes: All inducers and substrates were administered orally unless specified otherwise. All substrates were administered as a single dose unless specified otherwise. Inducer was dosed once daily unless specified otherwise. Where available, intravenous (IV) dosing of substrate drug is provided along with oral DDI to substantiate contribution of intestinal P-gp induction. To calculate % AUC ↓, $AUC_{0\rightarrow inf}$ (single dose) or $AUC_{0\text{-}tau}$ (multiple dosing) was preferred over $AUC_{0\rightarrow t}$ wherever possible.

[a] $AUC_{0\rightarrow t}$ was used to calculate % ↓ in AUC. % ↓ in AUC, C_{max} and $t_{1/2}$ were calculated using arithmetic mean unless specified otherwise.

[b] Geometric mean used to calculate % ↓ in AUC and C_{max}.

↔, no significant change concluded in study.

* Lutz et al. data not published. NR, not reported.

Staggered represents substrate not concomitantly administered with inducer during induction phase or administered after the last dose of an inducer. Concomitant means substrate was concomitantly given with the inducer in same time frame (within minutes); either during or on the last day of the induction phase. Dabigatran etexilate is a pro-drug. Total dabigatran (unconjugated dabigatran + dabigatran glucuronides) was measured. Note: exposure ratios 0.8-1.25 are generally not considered clinically meaningful but are reported here whenever these reached statistical significance criteria defined in the study.

Table 2:

Clinical DDIs likely involving intestinal P-gp induction and modulation of other transporters and drug metabolizing enzymes.

Inducer (Dose and Pre-treatment Duration)	Substrate (Dose)	Dosing interval between substrate and inducer	No. of subjects	AUC (% ↓)	C_{max} (% ↓)	$t_{1/2}$ (% ↓)	Other transporters/ enzymes potentially involved in substrate disposition
Rifampin (600 mg/d)	Tenofovir alafenamide (Emtricitabine 200 mg and tenofovir alafenamide 25 mg/d x 28 d alone or with rifampin)	Concomitant	21	55[a,b]	50[b]	NR	BCRP, OATP1B, CES1, CatA
Carbamazepine (300 mg twice daily x 20d)	Tenofovir alafenamide (Emtricitabine 200 mg and tenofovir alafenamide 25 mg)	Concomitant	26	54[b]	57[b]	↔*	
Rifampin (600 mg/d x 7d)	Fexofenadine (25 mg)	Staggered (~12 h)	10	59[b]	51[b]	49	OATP1B1, OATP1B3, OATP2B1, OAT3
Rifampin (600 mg/d x 6d)	Fexofenadine (60 mg)	Staggered (<12 h)	24	47 – 63[c]	33-51[c]	↔	
Carbamazepine (100 mg three times daily x 6d)	(S)-Fexofenadine (Fexofenadine 60 mg)	Concomitant on day 7 with carbamazepine (100 mg)	12	60[b]	31[b]	24	
	(R)-Fexofenadine (Fexofenadine 60 mg)			51[b]	32[b]	↔	
Carbamazepine (100 mg three times daily x 6d)	Fexofenadine (60 mg)	Concomitant on day 7 with carbamazepine (100 mg)	12	39[a,b]	35[b]	↔	
St John's wort (300 mg three times daily x 14d)	Fexofenadine (60 mg)	Concomitant (1 hr after morning dose of St. John's wort)	12	↔	↔	↔	
St John's wort (300 mg three times daily x 9d)	Fexofenadine (60 mg)	Concomitant	30[c]	32-50	NR	↔	
St John's wort LI160 (300 mg Jarsin 300® three times daily x 12d)	Fexofenadine (180 mg)	Staggered (next day)	20	47	37	↔	
Efavirenz (600 mg/d x 14d)	Fexofenadine (60 mg)	Staggered (~12 h)	12	↔[f]	↔	↔	
Apalutamide (240 mg/d x 28d)	Fexofenadine (30 mg)	NR	21	30[b]	↔	NR	
Danshen extract (1000 mg three times daily x 10d)	Fexofenadine (60 mg)	Concomitant with Danshen (1 g)	12	46[b]	35[b]	↔	
Rifampin (600 mg/d x 10d)	Sofosbuvir (400 mg)	Concomitant	17	72[b]	77[b]	↔*	BCRP, CatA, CES1
Carbamazepine (300 mg twice daily x 10d)		Staggered (~12 h)	24	48[b]	48*[b]	↔*	
Rifabutin (300 mg/d x 11d)		Staggered (~12 h)	20	24[b]	36*[b]	↔*	

Inducer (Dose and Pre-treatment Duration)	Substrate (Dose)	Dosing interval between substrate and inducer	No. of subjects	AUC (% ↓)	C_{max} (% ↓)	$t_{1/2}$ (% ↓)	Other transporters/ enzymes potentially involved in substrate disposition
Rifampin (600 mg/d x 17d)	Glecaprevir (300 mg)	Staggered (24 h)	12	88[b]	86[b]	NR	BCRP, OATP1B1, OATP1B3, CYP3A (minor)
	Pibrentasvir (120 mg)			87[b]	83[b]	NR	BCRP
Carbamazepine (200 mg twice daily x 20d)	Glecaprevir[e] (300 mg)	NR	10	66[b]	67[b]	NR	
	Pibrentasvir (120 mg)			51[b]	50[b]	NR	
Rifampin (600 mg/d x 7d)	Ledipasvir[e] (Ledipasvir 90 mg, Vedroprevir 200 mg and Tegobuvir 30 mg)	Staggered (next day)	31	59[b]	35[b]	17[d]	BCRP
Rifampin (600 mg/d x 7d)	Velpatasvir[e] (100 mg)	Staggered (next day)	12	82[b]	71[b]	NR	BCRP, CYP3A4, CYP2B6, CYP2C8 (metabolism minor)
Rifampin (600 mg/d x 7d)	Voxilaprevir (100 mg)	Staggered (12 hr)	24	73[b]	↔	NR	BCRP, OATP1B, CYP3A4
Rifampin (600 mg/d x 5d)	Celiprolol (200 mg)	Staggered (~14 h)	10	56[a,d]	↔[g]	↔	OATP2B1, OATP1A2, minimal metabolism
Rifampin (600 mg/d x 7d)	Afatinib (40 mg)	Staggered (~12 h)	22	34[b]	22[b]	↔	BCRP, minimal metabolism
Rifampin (600 mg/d x 5d)	Aliskiren (150 mg)	Staggered (12 h)	12	56[b]	39[b]	↔	OATP2B1, OATP1A2, CYP3A4 (minor)
Rifampin (600 mg/d x 6d)	Edoxaban (60 mg)	Concomitant on day 7 of rifampin	34	35[b]	↔	52	CES1, CYP3A (minor)
Rifampin (600 mg/d x 7d or 9d)	Apixaban (5 mg IV)	Staggered on day 8 of rifampin	20	39[b]	NR	49	BCRP, CYP3A4 (major)
	Apixaban (10 mg)	Staggered on day 10 of rifampin	20	54[b]	42[b]	↔	
Rifampin (150-450 mg days 1-3 and 600 mg days 4-7 once daily)	Rivaroxaban (20 mg)	NR	20	49[b]	22[b]	47[b]	BCRP, CYP3A, CYP2J2

All data were obtained from University of Washington Drug Interaction Solutions database, product prescribing information, and Drugs@FDA Clinical Pharmacology reviews.

Notes: All inducers and substrates were administered orally. All substrates were administered as a single dose unless otherwise specified. Inducer was dosed once daily unless specified otherwise. To calculate % AUC ↓, $AUC_{0\rightarrow inf}$ was preferred over $AUC_{0\rightarrow t}$ wherever possible.

[a] $AUC_{0\rightarrow t}$ was used to calculate % ↓ in AUC. % ↓ in AUC, C_{max} and $t_{1/2}$ were calculated using arithmetic mean unless specified otherwise.

[b] Geometric mean used to calculate % ↓ in AUC and C_{max}.

[c] Fexofenadine data from four study groups (n=6/group, categorized based on age and sex).

[d] Median values used to calculate % ↓ in AUC and C_{max}.

[e] Exposure decreases following multiple-doses of efavirenz-containing antiviral therapy not summarized due to mechanistic complexity of multidrug regimen.

[f] 27% decrease observed but was not statistically significant.

[g] 34% decrease observed but was not statistically significant.

↔, no significant change concluded in study.

[*] Lutz et al. data not published. NR, not reported.

Staggered represents substrate not concomitantly administered with inducer during induction phase or administered after the last dose of an inducer. Concomitant means substrate was concomitantly given with the inducer in same time frame (within minutes); either during or on the last day of the induction phase. Note: exposure ratios 0.8-1.25 are generally not considered clinically meaningful but are reported here whenever these reached statistical significance criteria defined in the study.

Table 3:

Clinical DDIs hypothesized to involve hepatic OATP1B induction, as well as modulation of other transporters and drug metabolizing enzymes.

Inducer (Dose and Pre-treatment Duration)	Substrate (Dose)	Dosing interval between substrate and inducer	No. of subjects	AUC (% ↓)	C_{max} (% ↓)	$t_{1/2}$ (% ↓)	Other transporters/enzymes potentially involved in substrate disposition
Rifampin (2 mg/d x 14d)	Rosuvastatin (10 mg)	Staggered (~12 h)	20	12[a]	↔	↔*	BCRP, NTCP, OATP2B1, MRP2, MRP4, OAT3, UGT1A1, UGT1A3
Rifampin (10 mg/d x 14d)				21[a]	15[a]	↔*	
Rifampin (75 mg/d x 14d)				54[a]	41[a]	~57*	
Rifampin (600 mg/d x 14d)				63[a]	30[a]	~48*	
Rifampin (450 mg/d x 6d)	Rosuvastatin (20 mg)	Staggered (~12 h)	18	↔	↔	↔	
Carbamazepine (300 mg, twice daily x 13d)	Rosuvastatin (10 mg)	Staggered (~12 h)	24	61[a]	61[a]	37*	
Apalutamide (240 mg/d x 36d)	Rosuvastatin (10 mg)	NR	21	41[a]	↔	NR	
Eslicarbazepine (1200 mg/d x 13d)	Rosuvastatin (40 mg)	Concomitant	33	37[a]	36[a]	↔	
Rifabutin (300 mg/d x 14d)	Rosuvastatin (10 mg)	Staggered (~12 h)	20	↔	26↑[a]	↔*	
Elagolix (300 mg twice daily)	Rosuvastatin (20 mg/d x 7d alone or with elagolix)	Concomitant	10	40[a]	↔	NR	
Rifampin (2 mg mg/d x 12d)	Pravastatin (20 mg)	Staggered (~12 h)	20	17[a]	14[a]	↔	MRP2, OAT3
Rifampin (10 mg/d x 12d)				19[a]	21[a]	↔	
Rifampin (75 mg/d x 12d)				58[a]	59[a]	~33	
Rifampin (600 mg/d x 12d)				58[a]	53[a]	↔	
Rifampin (600 mg/d x 5d)	Pravastatin (40 mg)	Staggered (17 h)	10	31	↔	↔	
Carbamazepine (300 mg, twice daily x 10d)	Pravastatin (20 mg)	Staggered (~12 h)	24	62[a]	65[a]	↔*	
Rifabutin (300 mg/d x 14d)	Pravastatin (20 mg)	Staggered (~12 h)	20	12[a]	↔[a]	↔*	
Efavirenz (600 mg/d x 11d	Pravastatin (40 mg/d x 4d alone or with efavirenz)	Concomitant	13	40[b,c]	18[c]	NR	
Rifampin (600 mg/d x 5d)	Coproporphyrin I (following rifampin multiple dose compared to that after single dose)	NA (no changes in coproporphyrin I and III baseline levels prior to single	12	52[b,d]	40	NA	MRP2, MRP3

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Inducer (Dose and Pre-treatment Duration)	Substrate (Dose)	Dosing interval between substrate and inducer	No. of subjects	AUC (% ↓)	C_{max} (% ↓)	$t_{1/2}$ (% ↓)	Other transporters/enzymes potentially involved in substrate disposition
	Coproporphyrin III (following rifampin multiple dose compared to that after single dose)	or the 6th dose of rifampin administration)		43[b,d]	39	NA	OATP2B1, MRP2, MRP3
Rifampin (600 mg/d x 10d)	Pitavastatin (4mg/d x 5d alone or with rifampin)	NR	18	29↑[a] (acid)	100↑[a]	88	BCRP, OATP2B1, MRP2, UGT1A3, UGT2B7
				58[a] (lactone)	17[a]	48	
Efavirenz (600 mg/d x 10d)	Pitavastatin (2mg/d x 4d alone or with efavirenz)	Concomitant	14	↔ (acid)	↔	NR	
				↔ (lactone)	↔	NR	
Rifampin (600 mg/d x 6d)	Glyburide (Glyburide 1.25 mg)	Staggered (~72 h)	9	65	53	58	P-gp, BCRP, OATP2B1, CYP2C9, CYP2C19, CYP3A
	4-Hydroxy glyburide (Glyburide 1.25 mg)			66	45	67	
	Glyburide (Glyburide 1.25 mg)	Concomitant (rifampin 600 mg IV + glyburide 1.25 mg oral, the day after induction regimen)		28	↔	60	
	4-Hydroxy glyburide (Glyburide 1.25 mg)			49	↔	57	
Rifampin (600 mg/d x 5d)	Glyburide (1.75 mg)	Staggered (12.5 h)	10	39	22	15	
Rifampin (600 mg/d x 7d)	Repaglinide (4 mg)	Staggered (24 h)	12	80[c]	79[c]	↔	CYP3A4, CYP2C8, UGT1A1/A3
	Repaglinide (Repaglinide 4 mg + Rifampin oral 600 mg)	Concomitant		48[c]	↔	↔	
	Repaglinide (4 mg)	Staggered (1 h)	8	32[a]	26[a]	56	
Rifampin (600 mg/d x 5d)	Repaglinide (0.5 mg)	Staggered (12.5 h)	9	57	41	27	
Rifampin (600 mg/d x 7d)	Simeprevir (200 mg/d x 7 d)	NR	18	48	31↑	NR	P-gp, MRP2, BCRP, CYP3A
Efavirenz (600 mg/d x 14d)	Simeprevir (150 mg/d x 14 d)	NR	23	71	51	NR	

All data were obtained from University of Washington Drug Interaction Solutions database, product prescribing information, and Drugs@FDA Clinical Pharmacology reviews.

Notes: All inducers and substrates, except endogenous coproporphyrin I and III, were administered orally. All substrates were administered as a single dose unless otherwise specified. Inducer was dosed once daily unless specified otherwise. To calculate % AUC ↓, $AUC_{0\rightarrow inf}$ was preferred over $AUC_{0\rightarrow t}$. % ↓ in AUC, C_{max} and $t_{1/2}$ were calculated using arithmetic mean unless specified otherwise.

[a] AUC and C_{max} changes were calculated based on geometric mean.

[b] $AUC_{0\rightarrow t}$ was used to calculate % ↓ in AUC.

[c] AUC and C_{max} changes were calculated based on median.

[d] Decrease (%) is relative to the DDI magnitude after single dose of rifampin

↔ no significant change concluded in study.

* Lutz et al. data not published. NR, not reported. NA, not applicable.

Staggered represents substrate not concomitantly administered with inducer during induction phase or administered after the last dose of an inducer. Concomitant means substrate was concomitantly given with the inducer in same time frame (within minutes); either during or on the last day of the induction phase. Note: exposure ratios 0.8-1.25 are generally not considered clinically meaningful but are reported here whenever these reached statistical significance criteria defined in the study.