Supplemental Materials

Induction of Human Intestinal and Hepatic Organic Anion Transporting Polypeptides; Where is the Evidence for its Relevance in Drug-Drug Interactions?

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Table S1

Drug interaction between itraconazole with pravastatin compared to coproporphyrin isomers and digoxin

PO Itraconazole dose		Probe		% Increase in probe AUC	Reference
Dose (mg)	Duration	Dose (mg)	Timing of dose after itraconazole last dose[a]		
200	5 days	PO Pravastatin (40)	4 hr	49	Mazzu et al., 2000
200	4 days	PO Pravastatin (40)	2 hr	72	Neuvonen et al., 1998
200	30 days	PO Pravastatin (40)	Co-dose	12	Jacobson, 1997
200	8 days	Coproporphyrin I	N/A	6	Shen et al., 2018
		Coproporphyrin III	N/A	9	
200	5 days	PO Digoxin (0.5)	1 hr	68	Jalava et al., 1997

N/A: not applicable

[a]Plasma T_{max} of itraconazole = 3-4 hr (Harden et al., 1988).

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Table S2

Clinical assessment of rifampicin as inhibitor of CYP3A and Pgp; digoxin and dabigatran etexilate as Pgp probes; and midazolam as CYP3A probe

Oral rifampicin dose (mg)	Oral probe drug (dose)	Probe dose timing vs rifampicin dose	% Increase in probe plasma AUC	Reference
600	Digoxin (0.5 mg)	Co-dose	29.9	Kirby et al., 2012
600	Digoxin (0.5 mg)	1 hr after rifampicin	46.2	Reitman et al., 2011
600	DABE (0.375 µg)[a]	Co-dose	132[a]	Prueksaritanont et al., 2017
600	Midazolam (33 µg)	Co-dose	14.7	Maeda et al., 2011
600	Midazolam (0.07 mg)	Co-dose	21.3	Yoshikado et al., 2017
600	Midazolam (10 µg)	Co-dose	5.6	Prueksaritanont et al., 2017

[a]Dosed as dabigatran etexilate (DABE) prodrug but DDI reported out as AUC of parent drug dabigatran.

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Table S3

Rifampicin and its metabolites as solute carrier, Pgp and MRP2 substrates in vitro (Pfizer, unpublished data)

Substrate (Conc.)	Uptake ratio in HEK293 cells (vs mock HEK293 cells)[a]			
	NTCP	OATP2B1	OATP1B3	OATP1B1
Rifampicin (RIF) (0.2 µM)	1.1 ± 0.2	0.6 ± 0.1	**2.5 ± 0.1**	**3.1 ± 0.1**
3-Formyl RIF (0.2 µM)	1.1 ± 0.2	0.5 ± 0.1	**5.5 ± 0.9**	**4.6 ± 1.0**
25-Desacetyl RIF (0.2 µM)	1.0 ± 0.1	0.6 ± 0.2	**19 ± 1.7**	**23 ± 1.0**
3-Formyl/25-Desacetyl RIF (0.2 µM)	1.1 ± 0.1	0.5 ± 0.2	**32 ± 0.6**	**37 ± 3.4**
Taurocholic acid (0.2 µM)	**70.1 ± 10.6**	-[b]	**-**	**-**
Rosuvastatin (1 µM)	**-**	**8.2 ± 0.7**	**72.2 ± 18.2**	**97.9 ± 4.0**

[a]Mean ± SD of n = 3 determinations. [b]Not determined. **Uptake ratio > 2 indicates compound is a substrate.**
OATP, organic anion transporting polypeptide; NTCP, sodium-dependent taurocholate co-transporting polypeptide.

Substrate (2 µM)	MDCK cell line (transwell B-A/A-B flux ratio)[a]	
	MDCK cells expressing Pgp	MDCK cells expressing MRP2
Rifampicin (RIF)	**29.4, 21.3**	**36.1, 17.9**
3-Formyl RIF	**175, 51.4**	**64.2, 18.0**
25-Desacetyl RIF	**56.3, 54.7**	**5.5, 2.4**
3-Formyl/25-Desacetyl RIF	**101**[b]	**3.5**[b]

[a]Values for two different experiments shown. B-A, basolateral-to-apical flux; A-B, apical-to-basolateral flux. **For MRP2 cell line, B-A/A-B ratio > 2 indicates compound is a substrate** (all ratios reduced to ~1.0 with MRP2 inhibitor MK571, 0.1 mM). **For Pgp cell line, compound is designated as substrate if B-A/A-B ratio > 6**; quinidine (2 µM) as positive control (B-A/A-B ratio = 125) and sertraline as negative control (B-A/A-B ratio = 3.2).
[b]Only one experiment was attempted.
Pgp, P-glycoprotein; MRP2, multidrug resistance-associated protein 2.

Table S4

Impact of various known CYP3A inducers on the PK of Pgp probe drugs digoxin and dabigatran

Object	Object	Precipitant	Precipitant	% Change AUC	Object Dose	Precipitant Dose
digoxin	Oral	phenytoin	Oral	-22.8	0.4 mg	0.2 g (7 days)
digoxin	Oral	phenytoin	Oral	-22.8	1 mg iv on day 1 and 0.4 mg po for 7 days (8 days)	0.2 g (8 days)
digoxin	Oral	rifampin	Oral	-30.4	0.25 mg	300 mg (7 days)
digoxin	Oral	rifampin	Oral	-30.3	1 mg	600 mg/day (10 days)
digoxin	Oral	rifampin	Oral	-21.1	0.5 mg	600 mg (14 days)
digoxin	Oral	rifampin	Oral	-18.2	0.5 mg	600 mg/day (6 days)
digoxin	Oral	rifampin	Oral	-16	0.5 mg	300 mg (7 days)
digoxin	Oral	rifampin	Oral	-15.6	0.4 mg	300 mg (7 days)
digoxin	Oral	st. John's wort	Oral	-28	0.2-0.3 loading dose followed by maintenance dose (21 days)	4 g encapsulated
digoxin	Oral	st. John's wort	Oral	-28	0.25 mg	300 mg (14 days)
digoxin	Oral	st. John's wort	Oral	-26.7	0.2-0.3 loading dose followed by maintenance dose (21 days)	hyperforin-rich extract
digoxin	Oral	st. John's wort	Oral	-25	0.25 mg (15 days)	300 mg (extract) (10 days)
dabigatran	Oral	carbamazepine	Oral	-31.8	75 mg (as dabigatran etexilate)	300 mg (26 days)
dabigatran	Oral	rifabutin	Oral	-24.9	75 mg (as dabigatran etexilate)	300 mg (26 days)
dabigatran	Oral	rifampin	Oral	-71.6	75 mg (as dabigatran etexilate)	600 mg (17 days)
dabigatran	Oral	rifampin	Oral	-67	150 mg	600 mg (8 days)
dabigatran	Oral	rifampin	Oral	-61.5	75 mg (as dabigatran etexilate)	75 mg (17 days)
dabigatran	Oral	rifampin	Oral	-35.6	75 mg (as dabigatran etexilate)	10 mg (17 days)

Data obtained on line at https://didb.druginteractionsolutions.org/