IDENTIFICATION AND EVALUATION OF CLINICAL SUBSTRATES OF ORGANIC ANION TRANSPORTING POLYPEPTIDES 1B1 AND 1B3

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Abstract

Background

Organic anion transporting polypeptides (OATP) 1B1 and 1B3 facilitate the uptake of drugs and endogenous compounds into the liver. In recent years, the impact of these transporters on drug-drug interactions (DDIs) has become a focus of research, and the evaluation of their role in drug disposition is recommended by regulatory agencies worldwide. While sensitive substrates of OATP1B1/1B3 have been identified in the literature and probe drugs have been proposed by some regulatory agencies, there is no general consensus on the ideal *in vivo* substrate for clinical DDI studies as analysis may be confounded by contributions from other metabolic and/or transport pathways.

Objective

The aim of this work was twofold:

- Provide a thorough analysis of the available *in vitro* and *in vivo* data regarding OATP1B1/1B3 substrates
- Propose the most sensitive and selective probe markers of OATP1B1/1B3 activity

Results and Conclusions

Using *in vitro,* clinical and pharmacogenetic (PGx) data available from the University of Washington Drug Interaction Database (UW DIDB, www.druginteractioninfo.org), a total of 178, 37 and 88 substrates were initially analyzed, respectively. The *in vitro* dataset was reduced to 85 prospective substrates using the criteria of $K_m \leq 10$ µM and/or uptake ratio ≥ 2, while the clinical data set was reduced to 39 substrates based on the criteria of ≥ 20% inhibition observed. The PGx data set was filtered to 31 substrates using studies where a single *SLCO1B1* or *SLCO1B3* variant was studied and shown to have an effect on drug exposure. A total of 47 compounds identified using all three datasets were further investigated as possible clinical substrates – 44 drugs, two endogenous compounds (coproporphyrin I and III), and one molecular imaging probe. Of note, a significant number of substrates from the *in vitro* dataset had no clinical data available to evaluate the relevance of OATP1B1/1B3 *in vivo*. Of the 44 drugs selected, six showed high sensitivity, with observed AUC ratios > 5 following administration of a single dose of rifampin, a recommended inhibitor of OATP1B1/1B3, including asunaprevir (AUC ratio of 14.8), atorvastatin (12.0), grazoprevir (10.2; component of the combination drug Zepatier), and pitavastatin (6.7). However, except for pitavastatin, these sensitive substrates are also significantly metabolized by CYP3A. Nine drugs showed moderate sensitivity with AUC ratios between 2 and 5 when co-administered with rifampin, including rosuvastatin (AUC ratio of 4.7), pravastatin (4.6), and fimasartan (4.3). It is worth noting that most of the substrates identified in this extensive analysis are also substrates of drug metabolizing enzymes and other transporters, highlighting the current challenge of finding a selective probe marker to study the impact of new molecular entities on OATP1B1/1B3 activity *in vivo*.

Potential Clinical Substrate Identification

The UW DIDB was queried for all available *in vitro,* clinical DDI, and PGx studies with reference to OATP1B1/1B3. Multiple key-phrase queries were performed for each dataset to ensure that the most complete list of potential substrates was evaluated.

In Vitro Studies

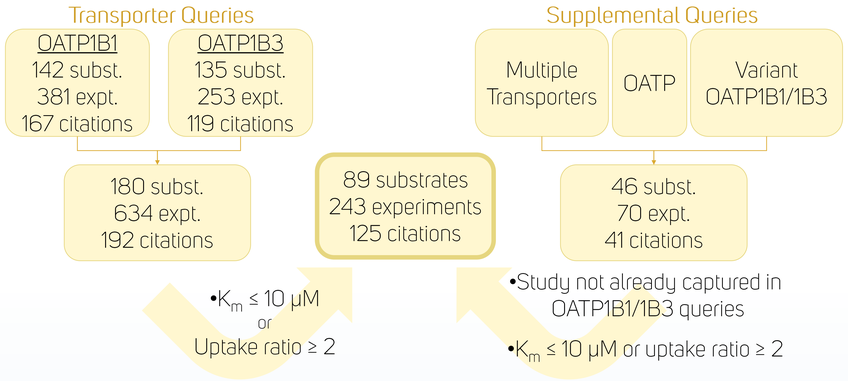


Figure 1. Substrate selection method for in vitro data. The UW DIDB was queried for in vitro studies involving OATP1B1/1B3. Data was then filtered for clinical relevance to remove any identified substrates that cannot be used in vivo. subst. – substrates, expt. – experiments.

Pharmacogenomic (PGx) Studies

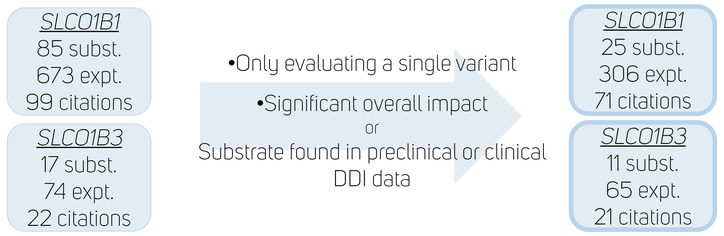
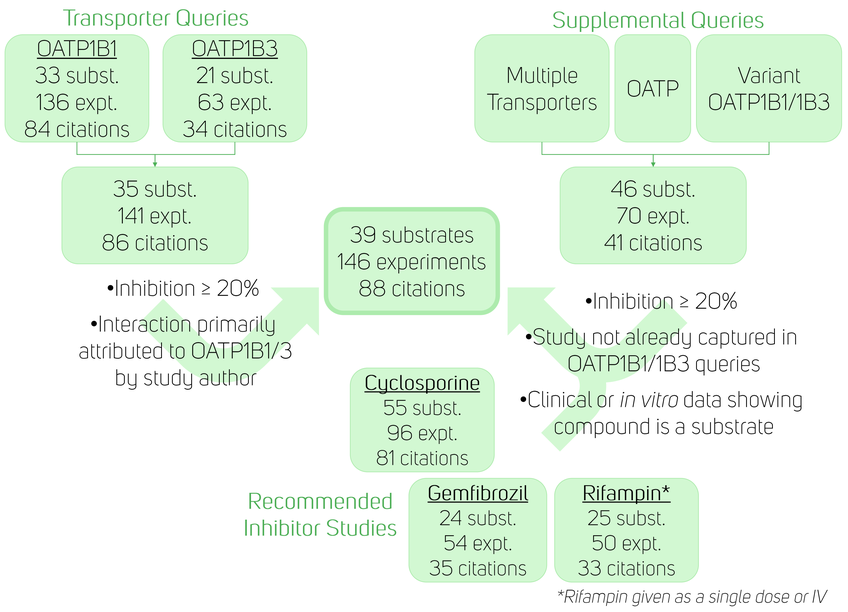


Figure 2. Substrate identification from PGx data. Studies evaluating the impact of SLCO1B1 /1B3 variants where the variant imparted a statistically significant clinical impact.

Clinical DDI Studies



*Rifampin given as a single dose or IV

Figure 3. Identification of clinical substrates from DDI studies. Queries identified those studies addressing the involvement of OATP1B1/1B3 or studies with a recommended inhibitor.

Results

Evaluation of Potential Substrates

- 53% of identified *in vitro* substrates did not have corresponding clinical data and were unable to be evaluated further.
- 15 substrates had *in vitro*, clinical DDI, and PGx data available
- 13 had *in vitro* and either clinical DDI or PGx data
- Overall, 47 potential substrates were identified and evaluated for clinical relevance
  - 44 drugs
  - 2 endogenous compounds
  - 1 PET probe - (15R)-^{11}C-TIC

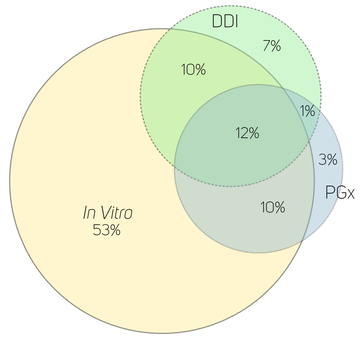


Figure 4. Overlap between data sources for identified potential substrates of OATP1B1/1B3, as percent of total substrates.

Potential Substrate Assessment

The two endogenous compounds, coproporphyrin I and coproporphyrin III, showed significant increases in exposure following co-administration of rifampin (4- and 3.4-fold, respectively).

Following identification, drugs were evaluated in two areas based on available data:

- Clinical substrate – OATP1B1/1B3 plays a significant role in the *in vivo* disposition of the drug
  - Magnitude of change in AUC following inhibition with a recommended inhibitor [rifampin, gemfibrozil, cyclosporine] or *SLCO1B1/1B3* genetic variant
  - *In vitro* data supporting the involvement of OATP1B1/1B3
  - Contribution of other metabolic and/or transport pathways

Potential Substrate Assessment (cont.)

- Clinical impact – for those drugs identified as substrates, inhibition of OATP1B1/1B3 may result in clinically meaningful safety issues.

Evaluation resulted in 30 drugs identified as clinical substrates:

- 18 showed a clinical impact of OATP inhibition
  - 6 sensitive substrates (AUC ratio ≥ 5, Table 1)
  - 9 moderate sensitive substrates (2 ≤ AUC ratio < 5)
- 12 have labeling recommendations regarding OATP1B1/1B3 inhibitors (Table 1)

Table 1. Substrates with labeling recommendations regarding OATP1B1/1B3 inhibition. Sensitive clinical substrates of OATP1B1/1B3 (AUC ratio ≥ 5 with a recommended inhibitor) are underlined and in bold. PGx data is for SLCO1B1 unless otherwise stated.

Substrate	Maximum AUC Ratio OATP1B Inhibition	PGx[a]	*In Vitro* Data	Label Recommendation	Other Significant Metabolism/ Transport
ambrisentan	1.9[b]	1.3	No	CsA (DR)	CYP3A/P-gp
asunaprevir	14.8[b]	--	Yes	RIF (C)	CYP3A/P-gp[g]
atorvastatin	12.0[b]	2.5	Yes	CsA (W)	CYP3A/P-gp[g], BCRP
bosentan	5.0[b,e]	--	Yes	CsA (C)	CYP3A/P-gp
eluxadoline	4.2[c]	2.0	Yes	OATP1B1 inhibitors (DR)	--
fluvastatin	3.6[c]	No Effect	Yes	CsA (DR), GEM (C)	CYP2C9, CYP3A, BCRP
grazoprevir	10.2[b]	--	Yes[f]	OATP1B1/1B3 inhibitors (C)	CYP3A/P-gp, BCRP
lovastatin	5.0[c]	2.9	Yes[f]	CsA (DR), GEM (DR)	CYP3A/P-gp[g]
paritaprevir	1.4[d]	--	Yes	RIF (C), GEM (C)	CYP3A/P-gp[g]
pitavastatin	6.7[b]	3.9	Yes	CsA (C), GEM (C), RIF (DR)	P-gp, BCRP
repaglinide	2.6[b]	2.9	Yes	CsA (W), GEM (C), RIF (W)	CYP2C8[g], CYP3A/ P-gp[g]
simvastatin	1.4[d]	3.2	Yes	GEM (C), CsA (C)	CYP3A/P-gp[g]

[a]studies with a statistically significant effect of the variant, evaluated by phenotype or genotype, [b]rifampin (RIF), [c]cyclosporine (CsA), [d]gemfibrozil (GEM), [e]increase observed in C_{min}, [f]qualitative data only, [g]AUC ratio with a specific inhibitor ≥ 5. DR – dose restriction, C – contraindication, W – warning.

Conclusions

- This work presents an early evaluation of the potential clinical substrates of OATP1B1/1B3. In-depth analysis of the available data is in progress to ensure the accurate description of the role of OATP1B1/1B3 in the disposition of the identified drugs.
- Comprehensive analysis of clinical and *in vitro* data resulted in the identification of 30 clinical substrates of OATP1B1/1B3
  - 50% show a clinically relevant impact to drug exposure following inhibition (AUC ratio ≥ 2)
  - 40% of identified compounds currently have labeling recommendations regarding OATP1B1/1B3 inhibitors
- Six substrates – asunaprevir, atorvastatin, grazoprevir, pitavastatin, bosentan, and lovastatin – showed the highest sensitivity to OATP1B1/1B3 inhibition (AUC ratio ≥ 5) and nine substrates, including pravastatin and rosuvastatin, showed moderate sensitivity (2 ≤ AUC ratio < 5).
- Lack of intersection between *in vitro,* and clinical datasets (DDI or PGx) highlights the limitations in current data reporting
- The high degree of overlap between OATP1B1/1B3 and CYP3A/P-gp substrates confounds precise determination of OATP1B1/3 contribution to clinical impact, highlighting the complex relationship between metabolic and transport processes
- Two endogenous compounds were identified in the selection process that show potential as novel biomarkers of OATP1B1/1B3 activity. Further data is needed to support the use of the substances as a replacement of extrinsic *in vivo* probes, however they represent an interesting approach for the future.
- To continue this work, an indexing system is in development to objectively assess the appropriateness of each identified substrate as a probe marker for OATP1B1/1B3 activity *in vivo*.

Acknowledgments

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