**Quantitative prediction of transporter- and enzyme-mediated clinical drug-drug interactions of OATP1B1 substrates using a mechanistic net-effect model**

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**Running title:** Mechanistic net-effect model for DDI predictions

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Supplementary Figure S1. Sensitivity analysis of the effect of empirical calibration factor for the *in vitro-in vivo* induction scaling (d-value, Eq. 9) on the model predictions of rifampicin based interactions. Closed squares and open circles represent predictions with d-value of 0.5 and 1, respectively.



Supplementary Figure S2. A proposed strategy for model-based predictions of transporter- and complex-DDIs associated with transporter-enzyme interplay. aDifferent cut-off may be considered for the significance of R-value based on the therapeutic index of the victim drug. bCut-off values for CYP interactions are given as suggested in the US FDA draft guidelines.(USFDA, 2012) cComplete mathematical expressions of the extended net-effect model is given in the Methods section.

Table S1. Summary of victim-cyclosporine DDI predictions using extended net-effect model.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Victim drug | Cyclosporine dose (mg) | Iu,max,in (μM) | Iu,gut (μM) | R-value | Fh` .(CLh-CLr)/ Fh .(CLh`-CLr`) | Fg`/Fg | Kpuu`/Kpuu | Predicted AUCR† | Observed AUCR | Supplementary References |
| Atorvastatin | 365 | 0.21 | 26.3 | 15.7 | 12.6 | 1.2 | 0.09 | 15.6 | 8.7 | (Hermann et al., 2004) |
| Atorvastatin | 175 | 0.10 | 12.6 | 8.1 | 7.3 | 1.1 | 0.15 | 8.3 | 15.3 | (Lemahieu et al., 2005) |
| Atorvastatin | 180 | 0.10 | 13.0 | 8.3 | 7.4 | 1.1 | 0.14 | 8.5 | 7.5 | (Asberg et al., 2001) |
| Bosantan | 300 | 0.17 | 21.6 | 13.1 | 4.0 | 1.0 | 0.27 | 4.0 | 3.7 | (Binet et al., 2000) |
| Cerivastatin | 200 | 0.11 | 14.4 | 9.1 | 5.8 | 1.1 | 0.18 | 6.3 | 3.8 | (Muck et al., 1999) |
| Cerivastatin | 200 | 0.11 | 14.4 | 9.1 | 5.8 | 1.1 | 0.18 | 6.3 | 4.8 | (Muck et al., 1999) |
| Fluvastatin | 100 | 0.06 | 7.2 | 5.0 | 5.2 | 1.0 | 0.20 | 5.2 | 3.6 | (Park et al., 2001) |
| Pitavastatin | 131 | 0.07 | 9.4 | 6.3 | 5.6 | 1.0 | 0.18 | 5.6 | 4.6 | (Hasunuma et al., 2003) |
| Pravastatin | 250 | 0.14 | 18.0 | 11.1 | 3.9 | 1.0 | 0.10 | 3.9 | 11.8 | (Park et al., 2002) |
| Pravastatin | 200 | 0.11 | 14.4 | 9.1 | 3.6 | 1.0 | 0.12 | 3.6 | 9.9 | (Hedman et al., 2004) |
| Rosuvastatin | 200 | 0.11 | 14.4 | 9.1 | 4.6 | 1.0 | 0.12 | 4.6 | 7.1 | (Simonson et al., 2004) |
| Repaglinide | 100 | 0.06 | 7.2 | 5.0 | 4.6 | 1.0 | 0.23 | 4.6 | 2.4 | (Kajosaari et al., 2005b) |

†after correcting in vitro CLint,h with drug-specific scaling factor.

Table S2. Summary of victim-gemfibrozil DDI predictions using extended net-effect model.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Victim drug | Gemfibrozil dose (mg) | Iu,max,in (μM) Gemfibrozil | Cu,max (μM) Gem-glu | R-value | Fh` .(CLh-CLr)/ Fh .(CLh`-CLr`) | Fg`/Fg | Kpuu`/Kpuu | Predicted AUCR | Observed AUCR | Supplementary References |
| Repaglinide | 30 | 0.3 | 0.3 | 1.2 | 2.0 | 1.0 | 1.66 | 2.0 | 1.8 | (Honkalammi et al., 2011a) |
| Repaglinide | 100 | 1.0 | 1.1 | 1.5 | 2.7 | 1.0 | 1.31 | 2.7 | 4.5 | (Honkalammi et al., 2011a) |
| Repaglinide | 300 | 3.0 | 3.2 | 2.6 | 4.5 | 1.0 | 0.81 | 4.5 | 6.7 | (Honkalammi et al., 2011a) |
| Repaglinide | 600 | 6.1 | 6.3 | 4.2 | 7.0 | 1.0 | 0.53 | 7.0 | 6.3 | (Honkalammi et al., 2011b) |
| Repaglinide | 900 | 9.1 | 9.5 | 5.8 | 9.3 | 1.0 | 0.40 | 9.3 | 8.3 | (Honkalammi et al., 2011a) |
| Repaglinide | 30 | 0.3 | 0.3 | 1.2 | 2.0 | 1.0 | 1.66 | 2.0 | 3.4 | (Honkalammi et al., 2012) |
| Repaglinide | 100 | 1.0 | 1.1 | 1.5 | 2.7 | 1.0 | 1.31 | 2.7 | 5.5 | (Honkalammi et al., 2012) |
| Repaglinide | 600 | 6.1 | 6.3 | 4.2 | 7.0 | 1.0 | 0.53 | 7.0 | 7.0 | (Honkalammi et al., 2012) |
| Repaglinide | 600 | 6.1 | 6.3 | 4.2 | 7.0 | 1.0 | 0.53 | 7.0 | 7.4 | (Kalliokoski et al., 2008) |
| Repaglinide | 600 | 6.1 | 6.3 | 4.2 | 7.0 | 1.0 | 0.53 | 7.0 | 8.1 | (Niemi et al., 2003) |
| Repaglinide | 600 (+itraconazole 100mg) | 6.1 | 6.3 | 4.2 | 26.9 | 1.0 | 0.80 | 26.9 | 19.3 | (Niemi et al., 2003) |
| Atorvastatin | 600 | 6.1 | 6.3 | 4.2 | 4.0 | 1.0 | 0.25 | 4.0 | 1.4 | (Backman et al., 2005) |
| Cerivastatin | 600 | 6.1 | 6.3 | 4.2 | 5.8 | 1.0 | 0.39 | 5.8 | 5.6 | (Backman et al., 2002) |
| Pravastatin | 600 | 6.1 | 6.3 | 4.2 | 2.7 | 1.0 | 0.25 | 2.9 | 2.0 | (Kyrklund et al., 2003) |
| Rosuvastatin | 600 | 6.1 | 6.3 | 4.2 | 3.0 | 1.0 | 0.25 | 3.1 | 1.9 | (Schneck et al., 2004) |

†after correcting in vitro CLint,h with drug-specific scaling factor.

Table S3. Summary of victim-rifampicin DDI predictions using extended net-effect model.

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Victim drug | Rifampicin dose (mg) | Condition(inh /ind)\* | Iu,max,in (μM) | Iu,gut (μM) | R-value | Fh` .(CLh-CLr)/ Fh .(CLh`-CLr`) | Fg`/Fg | Kpu`/ Kpu | Predicted AUCR† | Observed AUCR | Supplementary References |
| Repaglinide | 600 MD | inh+ind | 2.6 | 3.7 | 6.2 | 3.8 | 0.30 | 0.02 | 1.14 | 0.52 | (Bidstrup et al., 2004) |
| Repaglinide | 600 MD | inh+ind | 2.6 | 3.7 | 6.2 | 3.8 | 0.30 | 0.02 | 1.14 | 0.68 | (Hatorp et al., 2003) |
| Repaglinide | 600 MD | inh+ind | 0.4 | 0.0 | 1.7 | 1.2 | 0.26 | 0.06 | 0.32 | 0.43 | (Niemi et al., 2000) |
| Repaglinide | 600 MD | ind only | 0.0 | 0.0 | 1.1 | 0.8 | 0.26 | 0.09 | 0.20 | 0.20 | (Bidstrup et al., 2004) |
| Atorvastatin | 600 SD | inh only | 2.6 | 3.7 | 6.2 | 5.9 | 1.07 | 0.19 | 6.34 | 6.07 | (He et al., 2009) |
| Atorvastatin | 600 SD | inh only | 2.6 | 3.7 | 6.2 | 5.9 | 1.07 | 0.19 | 6.34 | 12.00 | (Maeda et al., 2011) |
| Atorvastatin | 600 SD iv | inh only | 2.6 | 0.0 | 6.2 | 5.9 | 1.00 | 0.19 | 5.92 | 7.25 | (Lau et al., 2007) |
| Atorvastatin | 600 MD | inh+ind | 0.4 | 0.0 | 1.7 | 1.3 | 0.12 | 0.02 | 0.15 | 0.20 | (Backman et al., 2005) |
| Bosantan | 600 MD | inh+ind | 0.4 | 3.7 | 1.7 | 0.7 | 0.56 | 0.03 | 0.41 | 0.42 | (van Giersbergen et al., 2007) |
| Pravastatin | 600 SD | inh only | 2.6 | 3.7 | 6.2 | 3.2 | 1.00 | 0.17 | 3.18 | 2.57 | (Deng et al., 2009) |
| Pravastatin | 600 SD | inh only | 2.6 | 3.7 | 6.2 | 3.2 | 1.00 | 0.17 | 3.18 | 4.64 | (Maeda et al., 2011) |
| Pitavastatin | 600 SD | inh only | 2.6 | 3.7 | 6.2 | 5.6 | 1.00 | 0.18 | 5.59 | 6.40 | (Chen et al., 2013) |
| Pitavastatin | 600 SD iv | inh only | 2.6 | 0.0 | 6.2 | 5.6 | 1.00 | 0.18 | 5.59 | 7.50 | (Prueksaritanont et al., 2014) |
| Pitavastatin | 600 SD | inh only | 2.6 | 3.7 | 6.2 | 5.6 | 1.00 | 0.18 | 5.59 | 5.70 | (Prueksaritanont et al., 2014) |
| Rosuvastatin | 450 MD | ind only | 0.0 | 3.7 | 1.0 | 1.0 | 1.00 | 1.00 | 1.02 | 0.94 | (Zhang et al., 2008) |
| Rosuvastatin | 600 SD | inh only | 2.6 | 3.7 | 6.2 | 3.8 | 1.00 | 0.17 | 3.81 | 3.00 | (Shen et al., 2013) |
| Rosuvastatin | 600 SD iv | inh only | 2.6 | 0.0 | 6.2 | 3.8 | 1.00 | 0.17 | 3.81 | 3.30 | (Prueksaritanont et al., 2014) |
| Rosuvastatin | 600 SD | inh only | 2.6 | 3.7 | 6.2 | 3.8 | 1.00 | 0.17 | 3.81 | 4.37 | (Prueksaritanont et al., 2014) |
| Glyburide | 600 MD | inh+ind | 2.6 | 3.7 | 6.2 | 2.1 | 0.46 | 0.02 | 0.99 | 0.78 | (Zheng et al., 2009) |
| Glyburide | 600 MD | ind only | 0.0 | 3.7 | 1.0 | 0.8 | 0.46 | 0.05 | 0.37 | 0.37 | (Zheng et al., 2009) |
| Glyburide | 600 MD | inh+ind | 0.4 | 3.7 | 1.7 | 1.2 | 0.46 | 0.03 | 0.53 | 0.61 | (Niemi et al., 2001a) |
| Glyburide | 600 SD | Inh only | 2.6 | 0.0 | 6.2 | 2.8 | 1.00 | 0.39 | 2.76 | 2.25 | (Zheng et al., 2009) |

\*Inhibition of OATP1B1 and/or induction of CYP3A4 were assumed based on the rifampicin dosage regimen. DDI studies involving single concomitant dosing of victim drug and rifampicin, only OATP1B1 inhibition by rifampicin was considered. In contrary, where victim drug was dosed within 12.5h after the last dose of rifampicin chronic pre-treatment (5- or 7-day), both OATP1B1 inhibition and CYP3A4 induction activity were assumed simultaneously; while when dosed after 12.5h only CYP3A4 induction was considered †after correcting in vitro CLint,h with drug-specific scaling factor. MD – multiple dose treatment. SD – single dose . †after correcting in vitro CLint,h with drug-specific scaling factor.

Table S4. Summary of victim-itraconazole/clarithromycin DDI predictions using extended net-effect model.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Victim drug | Perpetrator Dose (mg) | Iu,max,in (μM) | 4-OH-Itra Cu,max (μM) | R-value | Fh` .(CLh-CLr)/ Fh .(CLh`-CLr`) | Fg`/Fg | Kpuu`/Kpuu | Predicted AUCR† | Observed AUCR | Supplementary References |
| Itraconazole DDIs |  |  |  |  |  |  |  |  |  |  |
| Atorvastatin | 200 | 0.09 | 0.003 |  | 2.1 | 1.7 | 2.4 | 3.4 | 3.3 | (Kantola et al., 1998) |
| Atorvastatin | 200 | 0.09 | 0.003 |  | 2.1 | 1.7 | 2.4 | 3.4 | 2.5 | (Mazzu et al., 2000) |
| Cerivastatin | 200 | 0.09 | 0.003 |  | 1.5 | 1.3 | 1.2 | 2.0 | 1.3 | (Mazzu et al., 2000) |
| Fluvastatin | 100 | 0.04 | 0.002 |  | 1.3 | 1.0 | 1.2 | 1.3 | 1.3 | (Kivisto et al., 1998) |
| Pravastatin | 200 | 0.09 | 0.003 |  | 1.0 | 1.0 | 1.0 | 1.0 | 1.5 | (Mazzu et al., 2000) |
| Pravastatin | 200 | 0.09 | 0.003 |  | 1.0 | 1.0 | 1.0 | 1.0 | 1.7 | (Neuvonen et al., 1998) |
| Repaglinide | 100 | 0.04 | 0.002 |  | 1.2 | 1.1 | 1.2 | 1.2 | 1.4 | (Niemi et al., 2003) |
| Rosuvastatin | 200 | 0.09 | 0.003 |  | 1.0 | 1.0 | 1.0 | 1.0 | 1.4 | (Cooper et al., 2003) |
| Rosuvastatin | 200 | 0.09 | 0.003 |  | 1.0 | 1.0 | 1.0 | 1.0 | 1.3 | (Cooper et al., 2003) |
| Clarithromycin DDIs |  |  |  |  |  |  |  |  |  |  |
| Atorvastatin | 500 | 3.5 |  | 1.4 | 2.2 | 1.7 | 1.3 | 3.6 | 4.4 | (Jacobson, 2004) |
| Glyburide | 250 | 1.8 |  | 1.2 | 1.3 | 1.0 | 1.2 | 1.3 | 1.3 | (Lilja et al., 2007) |
| Pravastatin | 500 | 3.5 |  | 1.4 | 1.3 | 1.0 | 0.7 | 1.3 | 2.1 | (Jacobson, 2004) |
| Repaglinide | 250 | 1.8 |  | 1.2 | 1.3 | 1.1 | 1.0 | 1.4 | 1.4 | (Niemi et al., 2001b) |

†after correcting in vitro CLint,h with drug-specific scaling factor.

Table S5. References for the victim and perpetrator drug-related input parameters given in Table 1.

|  |  |
| --- | --- |
| Drugs | Supplementary References for input parameters |
| Atorvastatin | [CLiv - Pfizer Data on file] (Gibson et al., 1997) |
| Bosantan | (Weber et al., 1996; Weber et al., 1999; Obach et al., 2008) |
| Cerivastatin | (Muck et al., 1997; Obach et al., 2008; Varma et al., 2010) |
| Fluvastatin | (Tse et al., 1993; Lindahl et al., 1996) |
| Glyburide | (Rydberg et al., 1995; Jonsson et al., 2000; Obach et al., 2008; Varma et al., 2010; Varma et al., 2014) |
| Pitavastatin | (Yoshida et al., 2012) |
| Pravastatin | (Singhvi et al., 1990; Watanabe et al., 2009; Varma et al., 2012) |
| Rosuvastatin | (Crestor; Martin et al., 2003) |
| Repaglinide | (Hatorp et al., 1998; Plum et al., 2000; Kajosaari et al., 2005a; Varma et al., 2013a; Varma et al., 2013b) |
| Valsartan | (Flesch et al., 1997) |
| Cyclosporine | (Ptachcinski et al., 1985; Kurokawa et al., 1996; Tang et al., 2002; Bergman et al., 2006; Xia et al., 2007; Amundsen et al., 2010; Varma et al., 2010; Varma et al., 2012) |
| Gemfibrozil and Gemfibrozil-1-O-b-glucuronide | (Schneck et al., 2004; Ogilvie et al., 2006; Nakagomi-Hagihara et al., 2007; VandenBrink et al., 2011; Varma et al., 2012; Varma et al., 2013a) |
| Rifampicin | (Panchagnula et al., 2000; Varma et al., 2012; Varma et al., 2013b) |
| Clarithromycin | (Davey, 1991; Chu et al., 1992; Yago et al., 1996; Hirano et al., 2006; Watanabe et al., 2007) |
| Itraconazole and 4-OH-Itraconazole | (Heykants et al., 1989; Isoherranen et al., 2004; Varma et al., 2010) |
|  |  |

**Bioanalytical Procedure: LC-MS/MS methodology**

Analysis of 20µl samples was performed using high-performance liquid chromatography (Shimadzu DGU-14A membrane degasser, SCL-20A VP pump controller, LC-20AD VP pumps, and Sound Analytics ADDA autosampler) followed by tandem mass spectrometry (API 5500; MDS Sciex, Concord, ON, Canada) using a 2-min run time per sample. The mobile phase used to load the column (Kinetex C18 2.6u, 100A, 30x2mm) was 0.1% formic in water. Elution was performed at 0.7 min using a mobile phase of 0.1% formic acid in acetonitrile. The flow rate was set at 0.5 ml/min. The mass/charge ratio (m/z) and collision energies (electron volts) for each compound were as follows: atorvastatin m/z 559 440, 30eV; bosentan m/z 550 197, -45eV; cerivastatin m/z 460 356, 51eV; fluvastatin m/z 412  224, 45eV; pitavastatin m/z 442 290, 45eV; pravastatin m/z 423  101, -45eV; rosuvastatin m/z 482 258, 55eV; repaglinide m/z 453 230, 45eV; glyburide m/z 492 367, -20eV. The internal standard used in all analyses was tolbutamide in negative ion mode (m/z 269 > 170, -30eV) and carbamazapine in positive ion mode (m/z 237 > 194, 30eV).

**Derivation of Equation 2**

 For OATP substrates, hepatic clearance is determined by permeability-limited disposition, which is defined by extended-clearance term.







where PSuptake and PSefflux are the uptake and efflux intrinsic clearances across the sinusoidal membrane. PSinflux,active, PSefflux,active and PSpd are sinusoidal active uptake, active efflux and passive diffusion intrinsic clearances, respectively. CLint,CYP and CLint,bile are metabolic and biliary intrinsic clearances. SFactive represents empirical scaling factor for active uptake estimated by matching the *in vitro* CLint,h to the *in vivo* CLint,h, obtained from clinical pharmacokinetics. The primarily assumption here is accurate in vitro-in vivo translation of CLint,CYP and CLint,bile determined experimentally using HLM and SCHH systems.

Assuming active efflux across sinusoidal membrane (PSefflux,active) is negligible, above equation can be rewritten as:



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