Physiologically-based pharmacokinetic modeling of intestinal first-pass metabolism of CYP3A substrates with high intestinal extraction – supplementary material - Drug metabolism and Disposition (DMD #39248)

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TABLE 1

Summary of drug related parameters for used in the current PBPK model for 12 drugs investigated

<table>
<thead>
<tr>
<th>Drug</th>
<th>logP&lt;sub&gt;o:w&lt;/sub&gt;</th>
<th>pK&lt;sub&gt;a&lt;/sub&gt;</th>
<th>f&lt;sub&gt;u&lt;/sub&gt;&lt;sup&gt;o&lt;/sup&gt;</th>
<th>R&lt;sub&gt;b&lt;/sub&gt;</th>
<th>k&lt;sub&gt;a&lt;/sub&gt;</th>
<th>K&lt;sub&gt;m&lt;/sub&gt;</th>
<th>Solubility</th>
<th>Particle radius</th>
<th>P&lt;sub&gt;eff&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>4.07&lt;sup&gt;1&lt;/sup&gt;</td>
<td>4.46&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.051&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.61&lt;sup&gt;4&lt;/sup&gt;</td>
<td>3.7 ±1.8&lt;sup&gt;5&lt;/sup&gt;</td>
<td>33&lt;sup&gt;5&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
<td>Predicted</td>
</tr>
<tr>
<td>Buspirone</td>
<td>2.63&lt;sup&gt;1&lt;/sup&gt;</td>
<td>7.32, 4.12&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.05&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.81&lt;sup&gt;1&lt;/sup&gt;</td>
<td>5.0 ±0.71&lt;sup&gt;6&lt;/sup&gt;</td>
<td>2.3 ±1.3&lt;sup&gt;6&lt;/sup&gt;</td>
<td>8&lt;sup&gt;1&lt;/sup&gt;</td>
<td>-</td>
<td>Predicted</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>3.45&lt;sup&gt;1&lt;/sup&gt;</td>
<td>neutral</td>
<td>0.019&lt;sup&gt;6&lt;/sup&gt;</td>
<td>1.36&lt;sup&gt;5&lt;/sup&gt;</td>
<td>2.0 ±0.30&lt;sup&gt;4&lt;/sup&gt;</td>
<td>1.4&lt;sup&gt;4&lt;/sup&gt;</td>
<td>9.1 (13.3)&lt;sup&gt;7&lt;/sup&gt;</td>
<td>0.018&lt;sup&gt;8&lt;/sup&gt;</td>
<td>3.30&lt;sup&gt;9&lt;/sup&gt;</td>
</tr>
<tr>
<td>Felodipine</td>
<td>3.86&lt;sup&gt;1&lt;/sup&gt;</td>
<td>neutral</td>
<td>0.0048&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.70&lt;sup&gt;1&lt;/sup&gt;</td>
<td>2.8 ±0.9&lt;sup&gt;4&lt;/sup&gt;</td>
<td>5.3&lt;sup&gt;5&lt;/sup&gt;</td>
<td>-</td>
<td>1.87&lt;sup&gt;8&lt;/sup&gt;</td>
<td>Predicted</td>
</tr>
<tr>
<td>Indinavir</td>
<td>2.92&lt;sup&gt;1&lt;/sup&gt;</td>
<td>5.9, 3.7&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.36&lt;sup&gt;3&lt;/sup&gt;</td>
<td>0.84&lt;sup&gt;4&lt;/sup&gt;</td>
<td>1.8 ±0.4&lt;sup&gt;4&lt;/sup&gt;</td>
<td>0.1&lt;sup&gt;6&lt;/sup&gt;</td>
<td>90&lt;sup&gt;7&lt;/sup&gt;</td>
<td>-</td>
<td>Predicted</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>4.26&lt;sup&gt;1&lt;/sup&gt;</td>
<td>neutral</td>
<td>0.017&lt;sup&gt;7&lt;/sup&gt;</td>
<td>0.57&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.8&lt;sup&gt;1&lt;/sup&gt;</td>
<td>7.8&lt;sup&gt;7&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
<td>Predicted</td>
</tr>
<tr>
<td>Midazolam</td>
<td>3.25&lt;sup&gt;1&lt;/sup&gt;</td>
<td>6.1&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.031&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.55&lt;sup&gt;4&lt;/sup&gt;</td>
<td>4.2 ±0.7&lt;sup&gt;5&lt;/sup&gt;;</td>
<td>2.2 ±0.6&lt;sup&gt;6&lt;/sup&gt;</td>
<td>3.3&lt;sup&gt;7&lt;/sup&gt;</td>
<td>-</td>
<td>Predicted</td>
</tr>
<tr>
<td>Nisoldipine</td>
<td>3.80&lt;sup&gt;1&lt;/sup&gt;</td>
<td>neutral</td>
<td>0.0041&lt;sup&gt;2&lt;/sup&gt;</td>
<td>1.0&lt;sup&gt;8&lt;/sup&gt;</td>
<td>3.0 ±1.3&lt;sup&gt;4&lt;/sup&gt;</td>
<td>2.1&lt;sup&gt;8&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
<td>Predicted</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>4.10&lt;sup&gt;1&lt;/sup&gt;</td>
<td>8.2&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.028&lt;sup&gt;7&lt;/sup&gt;</td>
<td>0.74&lt;sup&gt;7&lt;/sup&gt;</td>
<td>2.5&lt;sup&gt;7&lt;/sup&gt;</td>
<td>0.3&lt;sup&gt;9&lt;/sup&gt;</td>
<td>64&lt;sup&gt;7&lt;/sup&gt;</td>
<td>-</td>
<td>Predicted</td>
</tr>
</tbody>
</table>
Effective permeability ($P_{\text{eff}}$) was predicted from $P_{\text{app}}$ (A-B) data (Gertz et al., 2010) and diffusion coefficients for cyclosporine, indinavir, saquinavir and terfenadine were predicted from molecular weights (Avdeef et al., 2004).

**Atorvastatin**: 1 (Ishigami et al., 2001; Lennernas, 2003); calculated from logD$_{pH 7}$ = 1.63; 2 (Lennernas, 2003); 3, 4 (Watanabe et al., 2010); 5 (Kantola et al., 1998a; Lilja et al., 1999; Mazzu et al., 2000; Fukazawa et al., 2004; Ando et al., 2005); 6 (Jacobsen et al., 2000)

**Buspirone**: 1 http://chem.sis.nlm.nih.gov/chemidplus/ (experimental); 2 (Mahmood and Sahajwalla, 1999); 3 (Gammans et al., 1986); 4 as in Gertz (2010); 5 solution: (Gammans et al., 1985) 6 tablet: (Barbhaiya et al., 1994; Henricsson, 1987; Lindholm et al., 1988; Yang and Elmquist, 1996; Akhlaghi et al., 1999); 7 as in Gertz (2010); 8 Neoral® (el Tayar et al., 1993; Lauerma et al., 1997; Lucangioli et al., 2003); 9 (Blychert et al., 1991); 10 current study

**Cyclosporine**: 1 (Valle et al., 1996; Kochansky et al., 2008); 2 (Ishigami et al., 1999); 3, 4, 5 (Lin et al., 1995; Glynn and Yazdanian, 1998); 6 as in Gertz (2010) provided by Pfizer Pharmacokinetics, Dynamics and Metabolism department (Sandwich, UK); 7 (Lauerma et al., 1997; Lucangioli et al., 2003); 8 (Henricsson, 1987; Lindholm et al., 1988; Yang and Elmquist, 1996; Akhlaghi et al., 1999); 9 as in Gertz (2010); 10 Neoral® (Mueller et al., 1994a; Mueller et al., 1994b; Ducharme et al., 1995; Edwards et al., 1999); 11 (Kivisto et al., 1997; Lamberg et al., 1998a; Lamberg et al., 1998c; Lamberg et al., 1998b; Lilja et al., 1998a; Dockens et al., 2006); 12 (Zhu et al., 2005)

**Indinavir**: 1 (Ishigami et al., 2001; Lennernas, 2003); calculated from logD$_{pH 7}$ = 1.63; 2 (Lennernas, 2003); 3, 4, 5 (Obach et al., 2008); 6 as in Gertz (2010) provided by Pfizer Pharmacokinetics, Dynamics and Metabolism department (Sandwich, UK); 7 (Lauerma et al., 1997; Lucangioli et al., 2003); 8 (Hart et al., 1995; Hsu et al., 1998; Sandhu et al., 2003); 9 current study; 10 current study supplemented by (Lin et al., 1995; Pathak et al., 2010)

**Lovastatin**: 1 http://chem.sis.nlm.nih.gov/chemidplus/ (experimental); 2 (Duggan et al., 1989); 3 as in Gertz (2010) provided by Pfizer Pharmacokinetics, Dynamics and Metabolism department (Sandwich, UK); 4 (Ishigami et al., 1999)

**Midazolam**: 1-2 (Gueorguieva et al., 2004; Rodgers and Rowland, 2006); 3 (Gertz et al., 2010); meta-analysis; 4 (Obach, 1999); 5 from solution: (Tsunoda et al., 1999; Rogers et al., 2003; Kharasch et al., 2004; Marciniak et al., 2006); 6 from tablets: (El Tayar et al., 2001; Vickers et al., 1990); 7 as in Gertz (2010); 8 Neoral® (Corsini et al., 1999); 9 (Glynn and Yazdanian, 1998); 10 (Duggan et al., 1989); 11 assumed to be 1; 12 (van Harten et al., 1988a; van Harten et al., 1988b; van Harten et al., 1988c; van Harten et al., 1989a; van Harten et al., 1989b; van Harten et al., 1989c; van Harten et al., 1989d; Baks et al., 1991; Bailey et al., 1993; Heining et al., 1999; Takanaga et al., 2000); 13 current study

**Nisoldipine**: 1 (Ishigami et al., 1999); 2 (Boelaert et al., 1988); 3 as in Gertz (2010); 4 (van Harten et al., 1988a; van Harten et al., 1988b; van Harten et al., 1988c; van Harten et al., 1989a; van Harten et al., 1989b; van Harten et al., 1989c; van Harten et al., 1989d; Baks et al., 1991; Bailey et al., 1993; Heining et al., 1999; Takanaga et al., 2000); 5 current study

**Simvastatin**: 1 (Ishigami et al., 2001; Lennernas, 2003); calculated from logD$_{pH 7}$ = 1.63; 2 (Lennernas, 2003); 3, 4, 5 (Watanabe et al., 2010); 6 (Kantola et al., 1998b; Lilja et al., 1999; Mazzu et al., 2000; Fukazawa et al., 2004; Ando et al., 2005); 7 (Jacobsen et al., 2000)

**Terfenadine**: 1 (Ishigami et al., 2001; Lennernas, 2003); calculated from logD$_{pH 7}$ = 1.63; 2 (Lennernas, 2003); 3, 4, 5 (Obach et al., 2008); 6 as in Gertz (2010) provided by Pfizer Pharmacokinetics, Dynamics and Metabolism department (Sandwich, UK); 7 (Lauerma et al., 1997; Lucangioli et al., 2003); 8 (Henricsson, 1987; Lindholm et al., 1988; Yang and Elmquist, 1996; Akhlaghi et al., 1999); 9 as in Gertz (2010); 10 Neoral® (Mueller et al., 1994a; Mueller et al., 1994b; Ducharme et al., 1995; Edwards et al., 1999); 11 (Lampen et al., 1995); 12 (Persson et al., 2005); 13 (Andrysek, 2003); 14 current study supplemented by (Chiu et al., 2003)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effective permeability ($P_{\text{eff}}$)</th>
<th>Predicted permeability ($P_{\text{app}}$)</th>
<th>Diffusion coefficient ($D_{\text{app}}$)</th>
<th>Metabolism</th>
<th>Other factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simvastatin</td>
<td>4.71$^1$ neutral 0.014$^2$ 0.57$^3$ 2.0 ±0.9$^4$ 3.4$^5$ - -</td>
<td>Predicted</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>3.26$^1$ neutral 0.013$^2$ 35$^3$ 2.6 ±0.7$^4$ 2.6$^5$ - -</td>
<td>Predicted</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Terfenadine</td>
<td>5.62$^1$ 9.7$^2$ 0.03$^3$ 1.0$^4$ 2.8$^5$ 1$^6$ 38$^7$ -</td>
<td>Predicted</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Terfenadine: ¹, ² (Avdeef and Berger, 2001); ³ (Benet et al., 1996); ⁴ assumed to be 1; ⁵ (Lalonde et al., 1996); ⁶ (Brown et al., 2007); ⁷ current study supplemented by (Avdeef, 2007)


