<table>
<thead>
<tr>
<th>DRUG</th>
<th>Half-Life (Hrs)</th>
<th>Time to Steady State (Hrs)</th>
<th>Metabolites</th>
<th>Time to Peak Conc. (Hrs)</th>
<th>Serum Predictability</th>
<th>Bioavailability</th>
<th>Serum Concentration (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUPRENORPHINE / NALOXONE</td>
<td>24-42/2-12</td>
<td>120-254</td>
<td>Norbuprenorphine</td>
<td>1.53-1.72 / 0.77-0.81</td>
<td>Y</td>
<td>15% / 3%</td>
<td>8/2mg: 3.37 +/- 1.8 and 0.193 +/- 0.0912</td>
</tr>
<tr>
<td>TRANSDERMAL BUPRENORPHINE</td>
<td>26</td>
<td>3 days</td>
<td>Norbuprenorphine</td>
<td>60</td>
<td>Y</td>
<td>15%</td>
<td>Mult. Dose: 10mcg/hr: 0.224 Single Dose: 5mcg/hr: 0.176 10mcg/hr: 0.191 20mcg/hr: 0.471</td>
</tr>
<tr>
<td>BUCCAL BUPRENORPHINE</td>
<td>27.6 +/-11.2</td>
<td>3 days</td>
<td>Norbuprenorphine</td>
<td>2.5-3</td>
<td>Y</td>
<td>46-65%</td>
<td>Mult. Dose: 60mcg: 0.077 +/-0.020 120mcg: 0.156 +/-0.044 300mcg: 0.47 +/-0.47 120mcg: 1.43 +/-0.45 240mcg: 0.364 +/-0.125</td>
</tr>
<tr>
<td>CODEINE</td>
<td>2.5-3.5</td>
<td>12.5-17.5</td>
<td>Morphine, Norcodeine, Normorphine, Hydrocodone, Codeine 6-glucuronide</td>
<td>1-2</td>
<td>Y</td>
<td>Well absorbed</td>
<td>IR 180mg = 222.9 +/- 48.9</td>
</tr>
<tr>
<td>TRANSDERMAL FENTANYL</td>
<td>16-25</td>
<td>72</td>
<td>Norfentanyl, 4-N-(N-propionylanilino) piperidine, 4-N-(N-hydroxypropionylanilino) piperidine, 1-(2-phenethyl)-4-N-(N-hydroxypropionylanilino) piperidine</td>
<td>24-72</td>
<td>Y</td>
<td>92%</td>
<td>25 mcg/hr: 0.6 +/-0.3 50mcg/hr: 1.4 +/- 0.5 75mcg/hr: 1.7 +/- 0.7 100mcg/hr: 2.5 +/- 1.2</td>
</tr>
<tr>
<td>TRANSNUCCAL, TRANSNUCCOSAL SUBLINGUAL FENTANYL**</td>
<td>14-19 (Onsolis) 2.6-11.7 (Fentora) 7 (Actiq) 5-13 (Abstral)</td>
<td>13-98</td>
<td>As above</td>
<td>0.75-4 (Onsolis) 0.58-0.78 (Fentora) 0.3-0.2 (Actiq) 0.25-1 (Abstral)</td>
<td>Y</td>
<td>Onsolis 71% Fentora 65% Actiq 47% Abstral 54%</td>
<td>800 mcg = 1.67* (Onsolis) 800 mcg = 1.59* (Fentora) 800 mcg = 1.03* (Actiq) 800 mcg = 1.42* (Abstral)</td>
</tr>
<tr>
<td>HYDROCODONE**</td>
<td>3.8</td>
<td>19-22.5</td>
<td>Hydromorphone, Norcodeine, 6-beta-hydrocodol, 6-alpha-hydrocodol, 6-beta-hydromorphol, 6-alpha-hydromorphol, normhydrocodeone</td>
<td>1.3</td>
<td>Y</td>
<td>Well absorbed</td>
<td>IR 10mg = 23.6ng +/-5.2</td>
</tr>
<tr>
<td>HEROIN</td>
<td>~3 min.</td>
<td>~15 min.</td>
<td>6-acetylmorphine, Morphine, Morphine-3-glucuronide, Normorphine, 6-acetylmorphine-3-glucuronide, Normorphine glucuronide</td>
<td>10 minutes for I.M. dose(^{6})</td>
<td>Y</td>
<td>Diacetylmorphone undergoes complete presystemic metabolism to morphine after oral administration</td>
<td>112mcg/min for 5 min Heroin level = 57 ng/mL C 6-acetylmorphine level=15ng/mL C</td>
</tr>
<tr>
<td>HYDROMORPHONE</td>
<td>2.5</td>
<td>12.5</td>
<td>Hydromorphone-3-glucuronide, Hydromorphone-3-glucoside, Diacetylmorphine-6-glucuronide, Diacetylmorphine-6-glucoside, Diacetylmorphine, Diacetylmorphine(^{5})</td>
<td>48-60 min.</td>
<td>Y</td>
<td>Variable: IM-57%</td>
<td>IR 48 mg = 19.7 +/- 4.04</td>
</tr>
<tr>
<td>LEVORPHANOL</td>
<td>1 dose: 11-16 Chronic: 30</td>
<td>72</td>
<td>3-glucuronide</td>
<td>approximately 1</td>
<td>?</td>
<td>100 mg IM = 551 ng/mL</td>
<td></td>
</tr>
<tr>
<td>Meperidine</td>
<td>~3.6</td>
<td>3-6 days</td>
<td>Normeperidin, meperidinc acid, normeperidinacacid</td>
<td>1-1.5</td>
<td>?</td>
<td>Variable: IM-57%</td>
<td>100 mg IM = 551 ng/mL</td>
</tr>
<tr>
<td>METHADONE</td>
<td>24</td>
<td>~5 days</td>
<td>EDDP (2-ethyl-1,5-dimethyl-3,3-diphenylpyrimolinium), EMDDP (2-ethyl-5-methyl-3,3-diphenylpyrline)</td>
<td>2-4</td>
<td>Y</td>
<td>Linear drug levels increase 260ng/mL for every 1mg/kg consumed</td>
<td>IR 40ng = 11.1 +/-8.4 CR 100mg = 36.9 +/-15.5</td>
</tr>
<tr>
<td>MORPHINE</td>
<td>2.4</td>
<td>24</td>
<td>Morphine-3-glucuronide, Morphine-6-glucuronide, Normorphine, 7,8-dihydromorphine, codeine (minor)</td>
<td>IR = 1 CR = 2-3</td>
<td>Y</td>
<td>80%</td>
<td>IR 40mg = 11.1 +/-8.4 CR 100mg = 36.9 +/-15.5</td>
</tr>
<tr>
<td>MORPHINE / NALTREXONE</td>
<td>29</td>
<td>145-203</td>
<td>As above + 6-beta-naltrexol</td>
<td>7.5</td>
<td>Y</td>
<td>20-40%</td>
<td>lower Cmax and a higher Cmin than conventional immediate-release morphine at steady-state</td>
</tr>
<tr>
<td>OXYCODONE</td>
<td>1,2,3,4</td>
<td>IV:IR=3.2 CR:R:45.8</td>
<td>IR: 17.5 CR: 24-36</td>
<td>Noroxycodone, Oxymorphone, Oxycodol, Oxymorphol, Noroxycodyl</td>
<td>IR: 1.6 CR: 2.1-3.2 Y</td>
<td>60-87%</td>
<td>IV (0.14 mg/kg):34-38 IR 20mg = 15.6 +/-4.4 CR 20mg = 15.1 +/-4.7</td>
</tr>
<tr>
<td>OXYMORPHONE</td>
<td>4</td>
<td>20-28</td>
<td>Tapentadol-O-glucuronide, desmethyl tapentadol, hydroxyl tapentadol</td>
<td>1.25-1.5</td>
<td>Y</td>
<td>32%</td>
<td>IR 20mg: 4.39 +/-1.72 ER 20mg: 2.54 +/-1.35</td>
</tr>
<tr>
<td>TRAMADOL (M1 metabolite)(^{10})</td>
<td>5.6-6.7 (6.7-7) ER: 6.5-10 (7.5-11)</td>
<td>2 days</td>
<td>O-desmethyltramadol (M1)</td>
<td>IR: 1-2.3 (1.5-2.4) ER: 4-12 (5.15)</td>
<td>Y</td>
<td>10%(^{5})</td>
<td>85-95%</td>
</tr>
</tbody>
</table>

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Footnotes for Table Above
IR = Immediate Release Products, CR = Continous Release products, SS = Steady State
A-Hours, unless otherwise indicated
B-Can detect heroin and 6-acetyl morphine within 10-15 minutes of parenteral administration
C-Administered IV in a single patient over 180 minutes
** These products are not considered bioequivalent
D-Cumulative amount of fentanyl release from patch dose in 24 hours.

E-hydromorphone is 7,8-dihydromorphine: Please note that morphine metabolism to hydromorphone has been confirmed in 8 mammals other than humans. There is only data that correlates the conversion of morphine to hydromorphone in humans.29
F- The bioavailability of oxymorphone increases significantly in hepatically (up to 12 fold) and renally impaired (65% with creatinine clearance less than 30 ml/min) patients

*peak concentrations

References to Opioid Pharmacokinetics and Expected Metabolites

42. Enido professional Package Insert. Copyright © Enido Pharmaceuticals Inc. 2006