

## Opioid Pharmacokinetics and Expected Metabolites

DRUG	Half-Life (Hrs <sup>A</sup> )	Time to Steady State (Hrs <sup>A</sup> )	Metabolites	Time to Peak Conc. (Hrs <sup>A</sup> )	Serum Predict -ability	Bioavailability	Serum Concentration (ng/mL)
BUPRENORPHINE / NALOXONE <sup>44,45,46</sup> (Suboxone)	24-42/2-12	120-294	Norbuprenorphine	1.53-1.72 / 0.77-0.81	Y	15% / 3%	8 mg/2 mg – Cmax = 3.37 +/- 1.8 ng/mL and 193 +/-91.2 pg/mL
CODEINE <sup>13,14,24</sup>	2.5-3.5	12.5-17.5	Morphine, Norcodeine, Normorphine, Hydrocodone, Codeine 6-glucuronide	1-2	Y	Well absorbed	IR 180mg = 222.9 +/- 48.9
TRANSDERMAL FENTANYL <sup>7,8,9,24</sup>	16-25	72	Norfentanyl, 4-N-(N-propionylanilino) piperidine, 4-N-(N-hydroxypropionylanilino) piperidine, 1-(2-phenethyl)-4-N-(N-hydroxypropionylanilino) piperidine	24-72	Y	92%	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
TRANSBUCCAL, TRANSMUCOSAL SUBLINGUAL FENTANYL <sup>7**</sup>	14-19 (Onsolis) 2.6-11.7 (Fentora) 7 (Actiq) 5-13 (Abstral)	13-98	As above	0.75-4 (Onsolis) 0.58-0.78 (Fentora) 0.3-2 (Actiq) 0.25-1 (Abstral)	Y	Onsolis 71% Fentora 65% Actiq 47% Abstral 54%	800 mcg = 1.67* (Onsalis) 800 mcg = 1.59* (Fentora) 800 mcg = 1.03* (Actiq) 800 mcg = 1.42* (Abstral)
HYDROCODONE <sup>15,16,17,24,39,40,41</sup>	3.8	19-22.5	Hydromorphone, Norcodeine, 6-beta-hydrocodol, 6-alpha-hydrocodol, 6-beta-hydromorphol, 6-alpha-hydromorphol, norhydrocodone	1.3	Y	Well absorbed	IR 10mg = 23.6ng +/-5.2
HEROIN <sup>21,22,23,24</sup>	~3 min. 1.7-5.3 min	~15 min.	6-acetylmorphine, Morphine, Morphine-3-glucuronide, Normorphine, 6-acetylmorphine 3-glucuronide, Normorphine glucuronide	10 minutes for I.M. dose <sup>B</sup>	Y	Diacetylmorphine undergoes complete presystemic metabolism to morphine after oral administration	112mcg/min for 5 min Heroin level = 57 ng/mL <sup>C</sup> 6-acetylmorphine level=15ng/mL <sup>C</sup>
HYDROMORPHONE <sup>10,11,12,24</sup>	2.5	12.5	Hydromorphone-3-glucuronide, Hydromorphone-3-glucoside, Dihydroisomorphine-6-glucuronide, Dihydroisomorphine-6-glucoside, Dihydroisomorphine, Dihydromorphine <sup>E</sup>	48-60 min.	Y	24%	IR 48 mg = 19.7 +/- 4.04
LEVORPHANOL	One dose 11-16hr Chronic dosing up to 30 hrs	72hrs	3-glucuronide	approximately 1	?		
MEPERIDINE	~3.6	3-6 days	Normeperidine, meperidinic acid, normeperidinic acid	1-1.5	?	Variable IM-57%	100 mg IM = 551 ng/mL
METHADONE <sup>18,19,20,24</sup>	24	~5 days	EDDP (2-ethyl-1,5-dimethyl-3,-3-diphenylpyrrolinium), EMDP (2-ethyl-5-methyl-3,3-diphenylpyraline)	2-4	Y	85%	Linear drug levels increase 260ng/mL for every 1mg/kg consumed
MORPHINE <sup>4,5,6,24,25</sup>	2-4	24	Morphine-3-glucuronide, Morphine-6-glucuronide, Normorphine, Codeine, 7,8-dihydromorphinone	IR = 1 CR = 2-3	Y	20-40%	IR 40mg = 11.1 +/-8.4 CR 100mg = 36.9 +/-15.5

MORPHINE / NALTREXONE <sup>43</sup> (Embeda)	29	145-203	As above + 6-beta-naltrexol	7.5	Y	20-40%	lower Cmax and a higher Cmin than conventional immediate-release morphine at steady-state
OXYCODONE <sup>1,2,3,24</sup>	IV,IR=3.2 CR=4.5-8	IR = 17.5 CR = 24-36	Noroxycodone, Oxymorphone, Oxycodyl, Oxymorphol, Noroxycodyl	IR = 1.6 CR = 2.1-3.2	Y	60-87%	IV (0.14 mg/kg)=34-38 IR 20mg = 15.6 +/-4.4 CR 20mg = 15.1 +/-4.7
OXYMORPHONE <sup>42</sup>	IR = 7.2 -9.4hr ER 9.4 – 11.3	IR = 3-4 days ER = 3 days	Oxyorphone-3-glucuronide, 6-OH-oxymorphone,	IR = 30mins ER = 3 hrs	Y	10% <sup>F</sup>	IR 20mg = 4.39 +/-1.72 ER 20mg = 2.54 +/-1.35
TAPENTADOL	4	20-28	Tapentadol-O-glucoronide, desmethyl tapentadol, hydroxyl tapentadol	1.25-1.5	Y	32%	Cmax – 2.45 mcg/mL

IR = Immediate Release Products, CR = Continuous 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-Cummulative amount of fentanyl release from patch dose in 24 hours.  
E-hydromorphone is 7,8-dihydromorphinone: Please note that morphine metabolism to hydro-morphone has been confirmed in 8 mammals other than humans. There is only data that correlates the conversion of morphine to hydromorphone in humans.<sup>29</sup>  
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

1. Reder RF, Oshlack B, Miotto JB, Benziger DD, Kaiko RF. Steady-state bioavailability of controlled-release oxycodone in normal subjects. *Clin Ther.* 1996 Jan-Feb;18(1):95-105.
2. Kaiko RF, Benziger DP, Fitzmartin RD, et al. Pharmacokinetic-pharmacodynamic relationships of controlled release oxycodone. *Clin Pharmacol Ther.* 1996 Jan; 59(1):52-61.
3. Oxycodone - MICROMEDEX® Healthcare Series, Thomson MICROMEDEX, Greenwood Village, Colorado Copyright © 1974-2008.
4. Christup LL, Sjogren P, Jensen NH, Banning AM, Elbaek K, Ersboll A. Steady-state kinetics and dynamics of morphine in cancer patients: is sedation related to the absorption rate of morphine? *J Pain Symptom Manage.* 1999 Sep;18(3):164-173.
5. Gourlay GK, Cherry DA, Onley MM, et al. Pharmacokinetics and pharmacodynamics of twenty four hourly Kapanol compared to twelve-hourly Ms Contin in the treatment of severe cancer pain. *Pain* 69 (1997)295-302.
6. Morphine - MICROMEDEX® Healthcare Series, Thomson MICROMEDEX, Greenwood Village, Colorado Copyright © 1974-2008.
7. Fentanyl - MICROMEDEX® Healthcare Series, Thomson MICROMEDEX, Greenwood Village, Colorado Copyright © 1974-2011.
8. Portenoy RK, Southam MA, Gupta SK, et al. Transdermal Fentanyl for Cancer Pain. *Anesthesiology* 1993 Jan;78(1):36-43.
9. Ashburn MA, Odgden LL, Ahang J, et al. The pharmacokinetics of transdermal fentanyl delivered with and without heat. *J Pain.* 2003 Aug;4(6):291-7.
10. Hagen N, Thirlwell MP, Dhaliwal HS, et al. Steady-state pharmacokinetics of hydromorphone and hydromorphone-3-glucuronide in cancer patients after immediate and controlled release hydromorphone. *J Clin Pharmacol* 1995;35:37-44.
11. JJ Vallner, JT Stewart, JA Kotzan, EB Kirsten, and IL Honigberg. Pharmacokinetics and bioavailability of hydromorphone following intravenous and oral administration to human subjects. *Journal of Clinical Pharmacology*, 1981; 21:152-156.
12. Hydromorphone - MICROMEDEX® Healthcare Series, Thomson MICROMEDEX, Greenwood Village, Colorado Copyright © 1974-2008.
13. Band CJ, Band PR, Deschamps M, et al. Human pharmacokinetic study of immediate-release (codeine phosphate) and sustained-release (codeine contin) codeine. *J Clin pharmacol* 1994;34:938-943.
14. Codeine - MICROMEDEX® Healthcare Series, Thomson MICROMEDEX, Greenwood Village, Colorado Copyright © 1974-2008.
15. Cone EJ, Darwin WD, Gorodetzky CW, and Tan T. Comparative metabolism of hydrocodone in man, rat, guinea pig, rabbit, and dog. *Drug Metabolism and Disposition.* 1978 6(4):488-493.
16. Honigberg IL, Stewart JT. Radioimmunoassay of hydromorphone and hydrocodone in human plasma. *J Pharm Sci.* 1980 Oct;69(10):1171-3.
17. Hydrocodone - MICROMEDEX® Healthcare Series, Thomson MICROMEDEX, Greenwood Village, Colorado Copyright © 1974-2008.
18. Wolff K, Rostami-Hodjegan A, Hay AWM, et al. Population-based pharmacokinetic approach for methadone monitoring of opiate addicts: potential clinical utility. *Addiction.* 2000;95(12):1771-1783.
19. Wolff K, Sanderson M, Hay AWM, and Raistrick D. Methadone concentrations in plasma and their relationship to drug dosage. *Clinical Chemistry.* 1991; 37(2):205-209.
20. Methadone - MICROMEDEX® Healthcare Series, Thomson MICROMEDEX, Greenwood Village, Colorado Copyright © 1974-2008.
21. Inturrisi CE, Max MB, Foley KM, et al. The pharmacokinetics of heroin in patients with chronic pain. *N Engl J Med* 1984; 310:1213-7.
22. Rentsch, KM, Kullak-Ublick GA, Reichel C, et al. Arterial and venous pharmacokinetics of intravenous heroin subjects who are addicted to narcotics. *Clin Pharm Ther.* 2001 Sep;70(3):237-246.
23. Heroin - MICROMEDEX® Healthcare Series, Thomson MICROMEDEX, Greenwood Village, Colorado Copyright © 1974-2005.
24. McQuay HJ. "Opioid problems, and morphine metabolism and excretion." Pain Research and Nuffield Department of Anaesthetics University of Oxford, UK. 8 March 2005. <<http://www.jr2.ox.ac.uk/bandolier/booth/painpag/wisdom/c14.html#RTFTtoC44>>
25. Yeh SY, McQuinn RL, Gorodetzky CW. Biotransformation of morphine to dihydromorphinone and normorphine in the mouse, rat, rabbit, guinea pig, cat, dog, and monkey. *Drug Metab Dispos.* 1977 Jul-Aug;5(4):335-42.
26. Lalovic B, Kharasch E, Hoffer C, Risler L, Liu-Chen LY, Shen DD. Pharmacokinetics and pharmacodynamics of oral oxycodone in healthy human subjects: role of circulating active metabolites. *Clinical Pharmacology & Therapeutics.* 79(5):461-79, 2006 May.
27. Kalso E. Oxycodone. *Journal of Pain & Symptom Management.* 29(5 Suppl):S47-56, 2005 May.
28. Darbari DS, Minniti CP, Rana S, van den Anker J. Pharmacogenetics of morphine: Potential implications in sickle cell disease. *American Journal of Hematology.* 83(3):233-6, 2008 Mar.
29. Cone EJ, Heit HA, Caplan YH, Gourlay D. Evidence of morphine metabolism to hydromorphone in pain patients chronically treated with morphine. *J Anal Toxicol.* 2006 Jan-Feb;30(1):1-5.
30. Murray A, Hagen NA. Hydromorphone. *Journal of Pain & Symptom Management.* 29(5 Suppl):S57-66, 2005 May.
31. Hutchinson MR, Menelaou A, Foster DJ, Collier JK, Somogyi AA. CYP2D6 and CYP3A4 involvement in the primary oxidative metabolism of hydrocodone by human liver microsomes. *British Journal of Clinical Pharmacology.* 57(3):287-97, 2004 Mar.
32. Lugo RA, Satterfield KL, Kern SE. Pharmacokinetics of methadone. *Journal of Pain & Palliative Care Pharmacotherapy.* 19(4):13-24, 2005.
33. Prommer E. Oxymorphone: a review. [Review] [29 refs] [Journal Article. Review] *Supportive Care in Cancer.* 14(2):109-15, 2006 Feb.
34. Hydromorphone - MICROMEDEX® Healthcare Series, Thomson MICROMEDEX, Greenwood Village, Colorado Copyright © 1974-2008.
35. Meperidine - MICROMEDEX® Healthcare Series, Thomson MICROMEDEX, Greenwood Village, Colorado Copyright © 1974-2008.
36. Propoxyphene - MICROMEDEX® Healthcare Series, Thomson MICROMEDEX, Greenwood Village, Colorado Copyright © 1974-2008.
37. Latta, KS, Ginsber B, Barkin, RL. Meperidine: A Critical Review. *American Journal of Therapeutics.* (9) 53 – 68. 2002.
38. McNulty JP. Can levorphanol be used like methadone for intractable refractory pain? *Journal of Palliative Medicine.* November 2(10) 293-296 , 2007.
39. Baselt, R C. Disposition of Toxic Drugs and Chemicals in Man, Second Edition. Davis, Calif.: Biomedical Publications, 1982.
40. Physicians' Desk Reference, Forty-Eight Edition. Montvale, NJ: Medical Economics Data Production Company, 1994.
41. Goldberger, Bruce A. Opiates Abused Drugs Monograph Series. Ed. Caplan, Yale H. Irving, TX: Abbott Laboratories, 1994.
42. Endo professional Package Insert. Copyright © Endo Pharmaceuticals Inc. 2006
43. morphine/naltrexone - MICROMEDEX® Healthcare Series, Thomson MICROMEDEX, Greenwood Village, Colorado Copyright © 1974-2011.
44. buprenorphine/naloxone - MICROMEDEX® Healthcare Series, Thomson MICROMEDEX, Greenwood Village, Colorado Copyright © 1974-2011.
45. Mendelson J, Upton RA, Evrhart ET, et al. Bioavailability of sublingual buprenorphine. *J Clin Pharmacol* 1997; 37:31-37.
46. Kuhlman JJ, Lalani S, Maglulio J, et al. Human pharmacokinetics of intravenous, sublingual, and buccal buprenorphine. *J Analytical Toxicology* 1996; 20: 369-378.
47. Tapentadol - MICROMEDEX® Healthcare Series, Thomson MICROMEDEX, Greenwood Village, Colorado Copyright © 1974-2011.