

Opioid Pharmacokinetics and Expected Metabolites

TABLE 5

DRUG	Half-Life (Hrs ^A)	Time to Steady State (Hrs ^A)	Metabolites	Time to Peak Conc. (Hrs ^A)	Serum Predict -ability	Bioavailability	Serum Concentration (ng/mL)
BUPRENORPHINE / NALOXONE ^{44,45,46} (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 ^{13,14,24}	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 ^{7,8,9,24}	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 ^{7**}	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 ^{15,16,17,24,39,40,41}	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 ^{21,22,23,24}	~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 ^B	Y	Diacetylmorphine undergoes complete presystemic metabolism to morphine after oral administration	112mcg/min for 5 min Heroin level = 57 ng/mL ^C 6-acetylmorphine level=15ng/mL ^C
HYDROMORPHONE ^{10,11,12,24}	2.5	12.5	Hydromorphone-3-glucuronide, Hydromorphone-3-glucoside, Dihydroisomorphine-6-glucuronide, Dihydroisomorphine-6-glucoside, Dihydroisomorphine, Dihydromorphine ^E	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 ^{18,19,20,24}	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 ^{4,5,6,24,25}	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 ⁴³ (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 ^{1,2,3,24}	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 ⁴²	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% ^F	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.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

- | | |
|---|--|
| <ol style="list-style-type: none"> 1. Reder RF, Oshlack B, Miotto JB, Benziger DD, Kaiko RF. Steady-state bioavailability of controlled-release oxycodone in normal subjects. <i>Clin Ther.</i> 1996 Jan-Feb;18(1):95-105. 2. Kaiko RF, Benziger DP, Fitzmartin RD, et al. Pharmacokinetic-pharmacodynamic relationships of controlled release oxycodone. <i>Clin Pharmacol Ther.</i> 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? <i>J Pain Symptom Manage.</i> 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. <i>Pain</i> 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. <i>Anesthesiology</i> 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. <i>J Pain.</i> 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. <i>J Clin Pharmacol</i> 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. <i>Journal of Clinical Pharmacology</i>, 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. <i>J Clin pharmacol</i> 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. <i>Drug Metabolism and Disposition.</i> 1978 6(4):488-493. 16. Honigberg IL, Stewart JT. Radioimmunoassay of hydromorphone and hydrocodone in human plasma. <i>J Pharm Sci.</i> 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. <i>Addiction.</i> 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. <i>Clinical Chemistry.</i> 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. <i>N Engl J Med</i> 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. <i>Clin Pharm Ther.</i> 2001 Sep;70(3):237-246. | <ol style="list-style-type: none"> 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. <i>Drug Metab Dispos.</i> 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. <i>Clinical Pharmacology & Therapeutics.</i> 79(5):461-79, 2006 May. 27. Kalso E. Oxycodone. <i>Journal of Pain & Symptom Management.</i> 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. <i>American Journal of Hematology.</i> 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. <i>J Anal Toxicol.</i> 2006 Jan-Feb;30(1):1-5. 30. Murray A, Hagen NA. Hydromorphone. <i>Journal of Pain & Symptom Management.</i> 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. <i>British Journal of Clinical Pharmacology.</i> 57(3):287-97, 2004 Mar. 32. Lugo RA, Satterfield KL, Kern SE. Pharmacokinetics of methadone. <i>Journal of Pain & Palliative Care Pharmacotherapy.</i> 19(4):13-24, 2005. 33. Prommer E. Oxymorphone: a review. [Review] [29 refs] [Journal Article. Review] <i>Supportive Care in Cancer.</i> 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. <i>American Journal of Therapeutics.</i> (9) 53 – 68. 2002. 38. McNulty JP. Can levorphanol be used like methadone for intractable refractory pain? <i>Journal of Palliative Medicine.</i> 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. <i>J Clin Pharmacol</i> 1997; 37:31-37. 46. Kuhlman JJ, Lalani S, Maglulio J, et al. Human pharmacokinetics of intravenous, sublingual, and buccal buprenorphine. <i>J Analytical Toxicology</i> 1996; 20: 369-378. 47. Tapentadol - MICROMEDEX® Healthcare Series, Thomson MICROMEDEX, Greenwood Village, Colorado Copyright © 1974-2011. |
|---|--|