

Opioid Pharmacokinetics, Serum Predictability, and Expected Metabolites

DRUG	Half-Life (Hrs ^a)	Time to Steady State (Hrs ^a)	Metabolites	Time to Peak Conc. (Hrs ^a)	Serum Predictability	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%	8/2mg: 3.37+/-1.8 and 0.193+/-0.0912
TRANSDERMAL BUPRENORPHINE ⁴⁸	26	3 days	Norbuprenorphine	60	Y	15%	Mult. Dose: 10mcg/hr: 0.224 Single Dose: 5mcg/hr: 0.176 10mcg/hr: 0.191 20mcg/hr: 0.471
BUCCAL BUPRENORPHINE ^{48,49}	27.6+/-11.2	3 days	Norbuprenorphine	2.5-3	Y	46-65%	Mult. Dose: 60mcg q12h: 0.077+/-0.020 Single Dose: 75mcg: 0.17+/-0.30 120mcg q12h: 0.156+/-0.044 300mcg: 0.47+/-0.47 180mcg q12h: 0.216+/-0.106 1200mcg: 1.43+/-0.45 240mcg q12h: 0.364+/-0.125
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* (Onsolis) 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	1 dose: 11-16 Chronic: 30	72	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 ^{4,5,6,24,25,51} IR, CR (MS Contin)	2-4	24	Morphine-3-glucuronide, Morphine-6-glucuronide, Normorphine, 7,8-dihydromorphinone, codeine (minor)	IR = 1 CR = 2-3	Y	20-40%	IR 15mg q6h: • Cmax: 22.0 ± 1.0 • Cmin: 3.5 CR (MS Contin) 30mg q12h: • Cmax: 20.3 ± 1.0 • Cmin: 4.5
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

Developed by: Jeffrey Fudin, BS, PharmD, DAIPM, FCCP. FASHP
Rev 08-23-2017: Mena Raouf, PharmD

Morphine ER (Kadian) ⁵²	2-4	24	Morphine-3-glucuronide, Morphine-6-glucuronide, Normorphine, 7,8-dihydromorphinone, codeine (minor)	10.3 ± 3.3	Y	40%	100mg daily (steady-state) <ul style="list-style-type: none"> Cmax: 37.3 ± 14.0 Cmin: 9.9 ± 5.2
OXYCODONE ^{1,2,3,24,53} IR, CR (OxyContin)	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 5mg q6h: <ul style="list-style-type: none"> Cmax: 15.6 +/- 4.4 Cmin: 6.5 +/- 3.1 CR (OxyContin) 10mg q12h: <ul style="list-style-type: none"> Cmax: 15.1 +/- 4.7 Cmin: 6.2 +/- 2.6 CR (OxyContin) 40mg q12h fasted <ul style="list-style-type: none"> Cmax: 42.30 +/- 10.44 Cmin: 14.1 +/- 3.48 CR (OxyContin) 40mg q12h with high fat meal <ul style="list-style-type: none"> Cmax: 63.11 +/- 12.86 Cmin: 15.8 +/- 3.13
OXYCODONE ER (XTAMPZA) ⁵³	Fasted: 14 hours Low fat meal: 8.75 Medium fat meal: 6.8 High fat meal: 5.6	24-70	Noroxycodone, Oxymorphone, Oxycodyl, Oxymorphol, Noroxycodyl	3-3.7 hours (Fasted, low-medium fat meal) 6.23 hours (high fat meal)	Y	Fasted: 75% Fed: 114%	36mg q12h: Fasted: 31.5 +/- 9.5 with low fat meal: 37.5 +/- 9.57 with medium fat meal: 58 +/- 18.9 with high fat meal: 51.85 +/- 14.362
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 ^{47, 54}	IR : 4 ER: 5.2 +/- 1.0	20-28	Tapentadol-O-glucoronide, desmethyl tapentadol, hydroxyl tapentadol	IR: 1.25-1.5 ER: 5	Y	32%	IR 50mg single dose: <ul style="list-style-type: none"> Cmax: 54.6 +/- 19.6 Cmin: 27.3 +/- 9.9 100mg q6h <ul style="list-style-type: none"> Cmax: 118 +/- 33.1 Cmin: 59 +/- 16.6 ER single-dose: <ul style="list-style-type: none"> 50mg: 10.1 +/- 2.59 100mg: 25.5 + 6.38 200mg: 62.5 +/- 17.9 250mg: 89.3 +/- 28.1 ER multiple dose <ul style="list-style-type: none"> 250mg q12h: 132 +/- 35.1
TRAMADOL (M1 metabolite) ⁵⁰	IR: 5.6-6.7 (6.7-7) ER: 6.5-10 (7.5-11)	IR: 2 days ER: 4 days	O-desmethyiltramadol (M1)	IR: 1-2.3 (1.5-2.4) ER: 4-12 (5.15)	Y	IR: 75% ER: 85-95%	100mg IR q6h: 592 (110) 200mg ER qd: 332-345 (70-95)

Footnotes for Table Above

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

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#RTFTcC44>>
25. Yeh SY, McQuinn RL, Gorodetzky CW. Biotransformation of morphine to dihydromorphine 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, Magluilo 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.
48. Buprenorphine - MICROMEDEX® Healthcare Series, Thomson MICROMEDEX, Greenwood Village, Colorado Copyright © 1974-2016.
49. Bai SA, Xiang Q, Finn A. Evaluation of Pharmacokinetics of single- and multiple-dose buprenorphine buccal film in healthy volunteers. *Clin Ther.* 2016 Feb;38(2):358-69.
50. Tramadol - MICROMEDEX® Healthcare Series, Thomson MICROMEDEX, Greenwood Village, Colorado Copyright © 1974-2016.
51. Savarese JJ, Goldenheim PD, Thomas GB, Kaiko RF. Steady-State Pharmacokinetics of Controlled Release Oral Morphine Sulphate in Healthy Subjects. *Clin Pharmacokinet.* 1986 Nov-Dec;11(6):505-10.
52. Kadian (morphine sulfate) [prescribing information]. Irvine, CA: Allergan USA Inc; December 2016.
53. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/208090Orig1s000MedR.pdf
54. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/200533Orig1s000ClinPharmR.pdf