

OPIOIDS AND BENZODIAZEPINES: SAFE PRESCRIBING FOR MIDWIVES

Pharmaceuticals Used for Labour and Postpartum Pain Management

OPIOIDS USED IN LABOUR

Drug	Adult half-life ¹	Neonatal half-life ^{2,3}	Active metabolite ¹ (Y / N)	Crosses Placenta ^{1,4} (Y / N)	Safety Data (of medication near delivery) / Notes ^{1,4}
Morphine	2-4 h	9 h – morphine ³ 18 h – metabolite ³	Yes	Yes	Opioids given near delivery may cause respiratory depression in the neonate at birth. The risk increases with increased cumulative doses. Prolonged use in gestation may cause neonatal withdrawal.
Fentanyl	2-4 h	1-15 h ³	No	Yes	Opioids given near delivery may cause respiratory depression in the neonate at birth. The risk increases with increased cumulative doses. Prolonged use in gestation may cause neonatal withdrawal.
Meperidine (Demerol®)	2.5-4 h (active metabolite 15-30h)	23 h 30-85 h - active metabolite	Yes	Yes	Not recommended due to an active metabolite with a long half-life that can accumulate in both the neonate and the woman. Can cause seizures, respiratory distress, and impair neurobehavior of neonates. Prolonged use in gestation may cause neonatal withdrawal.

PHARMACEUTICALS USED IN POSTPARTUM

Drug	Adult half-life ¹	Neonatal half-life ^{1,2,3}	Relative Infant Dose(%) ^{12,13}	Metabolism ¹	Active metabolite(s) ¹	Suitable for breastfeeding ^{12,13}
Hydromorphone	2-3 h	unknown	0.67	Glucuronidation	No	Yes - preferred agent ¹
Codeine	3 h	morphine 4.5-13.3 h	0.6 - 8.1	CYP2D6	Yes [#] (half-life 2-4 hours)	No ^{*1}
Caffeine ^{&}	5 h	72-96 h	6 - 25.9	CYP1A2	No	In moderation
Acetaminophen [@]	2 (2-3) h	7 (4-10) h	8.8 - 24.2	Glucuronidation, sulfation	No	Yes
Oxycodone	3.7 (2-4) h	1.2-3 h	1-8	CYP2D6, CYP3A4	Yes	Not preferred ¹
Tramadol	6-8 h	3.6 h in children. No data in neonates	<10	CYP2B6, CYP2D6, CYP3A4	Yes (half-life 7-9 hours)	No [^]

[#]metabolized to morphine via CYP2D6

^{*}infant deaths have occurred⁴⁻⁸

¹apneas, respiratory depression, and excess sedation have occurred⁵⁻¹⁴

[&] Caffeine accelerates absorption and enhances the analgesic effect of acetaminophen.

[^] Recent reports of pediatric adverse effects (9 cases of breathing problems, including 3 deaths) have led to a new recommendation to avoid tramadol in lactation^{15,16}

[@] Acetaminophen is an effective medication for mild to moderate pain and improves the balance between analgesia and side effects of narcotics.

Note: Although hydromorphone is the preferred agent in lactation (no active metabolite, short half-life, low RID), this medication has been associated with neonatal opioid toxicity in lactation.¹⁴ All infants exposed to any opioid in lactation need to be monitored for signs of toxicity (e.g. sedation, respiratory depression/apneas, not waking to feed at regular intervals [change in pattern/poor feeding], constipation, urinary retention and weakness).^{12,13}

REVERSAL AGENTS

Drug	Adult half-life ¹	Neonatal half-life ^{2,3}	Active metabolite ¹ (Y / N)	Crosses placenta ^{1,4} (Y / N)	Suitable for breastfeeding ^{12,13}	Safety Data of medication near delivery & in lactation / Notes ^{4,12, 13}
<p>Naloxone (Narcan®)</p> <p>Antidote for opioids</p>	0.5 – 1.5 h	1.2 – 3 h	Unknown	Yes	<p>Yes – minimal amounts absorbed orally</p>	<p>Note: reversal effects of naloxone may end before opiate effects; repeated doses may be needed.</p> <p>Caution when used in woman with chronic narcotic use in pregnancy.</p> <p>Although the narcotic antagonist naloxone has previously been used in newborns with respiratory depression following maternal opiate exposure, there is insufficient evidence to evaluate the safety and efficacy of such a practice. See NRP guidelines for treatment of infants with respiratory depression at birth.</p> <p>If required for acute opioid overdose, consider "pumping and dumping" breastmilk until the client is alert and oriented, and opioid eliminated (depending on half-life).</p>

1. Lexicomp Online®, Lexi-Drugs®, Hudson, Ohio: Lexi-Comp, Inc.; February 2016.
2. Lexicomp Online®, Pediatric & Neonatal Lexi-Drugs®, Hudson, Ohio: Lexi-Comp, Inc.; February 2016.
3. NeoFax® 2010. 23rd edition. Montvale, NJ: Thomson Reuters; 2010.
4. Briggs GG, Freeman RK. Briggs’ Drugs in Pregnancy and Lactation, 10th edition. Philadelphia, PA: Wolters Kluwer Health; 2015.
5. Davis JM, Bhutari VK. Neonatal apnea and maternal codeine use. *Ped Res* 1985; 19(4):170.
6. Naumburg EG, Meny RG. Breast Milk Opioids and Neonatal Apnea. *The Pediatric Forum* 1998;142:11-12.
7. Koren G, Cairns J, Chitayat D, Gaedigk A, Leeder SJ. Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. *Lancet* 2006 Aug 19; 368(9536):704.
8. Lam J, Matlow JN, Ross CJ et al. Postpartum maternal codeine therapy and the risk of adverse neonatal outcomes: the devil is in the details. *Ther Drug Monit* 2012;34:378-80.
9. Lam J, Kelly L, Ciszkowski C, Landsmeer ML, Nauta M, Carleton BC, Hayden MR, Madadi P, Koren G. Central nervous system depression of neonates breastfed by mothers receiving oxycodone for postpartum analgesia. *J Pediatr*. 2012Jan;160(1):33-37.e2. Epub 2011 Aug 31. PubMed PMID: 21880331.
10. Timm NL. Maternal use of oxycodone resulting in opioid intoxication in her breastfed neonate. *J Pediatr* 2013;162:421-2.
11. Sulton-Villavasso C, Austin CA, Patra KP et al. Index of suspicion. Case1. Infant who has respiratory distress. *Pediatr Rev* 2012;33:279-284.

12. Hale TW, Rowe HE. Medications & Mothers' Milk 2014. 16th edition. Texas: Hale Publishing; 2014.
13. Hale TW, Rowe HE. Medications and Mothers' Milk 2017. 17th edition. New York, NY: Springer Publishing Company.
14. Schultz ML, Kostic M, Kharasch S. A case of toxic breast-feeding? *Pediatr Emer Care* 2017: doi: 10.1097/PEC.0000000000001009.
15. U.S. Food & Drug Administration. FDA drug safety communication: FDA restricts use of prescription codeine pain and cough medicines and tramadol pain medicines in children; recommends against the use in breastfeeding women. Available from URL: <https://www.fda.gov/Drugs/DrugSafety/ucm549679.htm>
16. Health Canada Health Product InfoWatch. Case report: international case of respiratory depression in a child with ultrarapid CYP2D6 metabolism after tramadol use. Nov 2015. Available from URL: http://www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/hpiw-ivps_2015-11-eng.php#ca
17. Caffeine accelerates absorption and enhances the analgesic effect of acetaminophen.
18. Acetaminophen is an effective medication for mild to moderate pain and improves the balance between analgesia and side effects of narcotics.