



The pharmacokinetics of drugs taken during breastfeeding for dentists

Wendy Jones PhD MRPharmS MBE

www.breastfeeding-and-medication.co.uk



Understanding of pharmacokinetics

- › Using pharmacokinetics we can evaluate the risk of the drug passing through breastmilk
- › Do we need to “manage” breastfeeding and would it help?
- › How do we support the mother to feed as she has chosen?
- › Breastmilk is about so much more than milk

Drug passing to baby vs risk of not breastfeeding

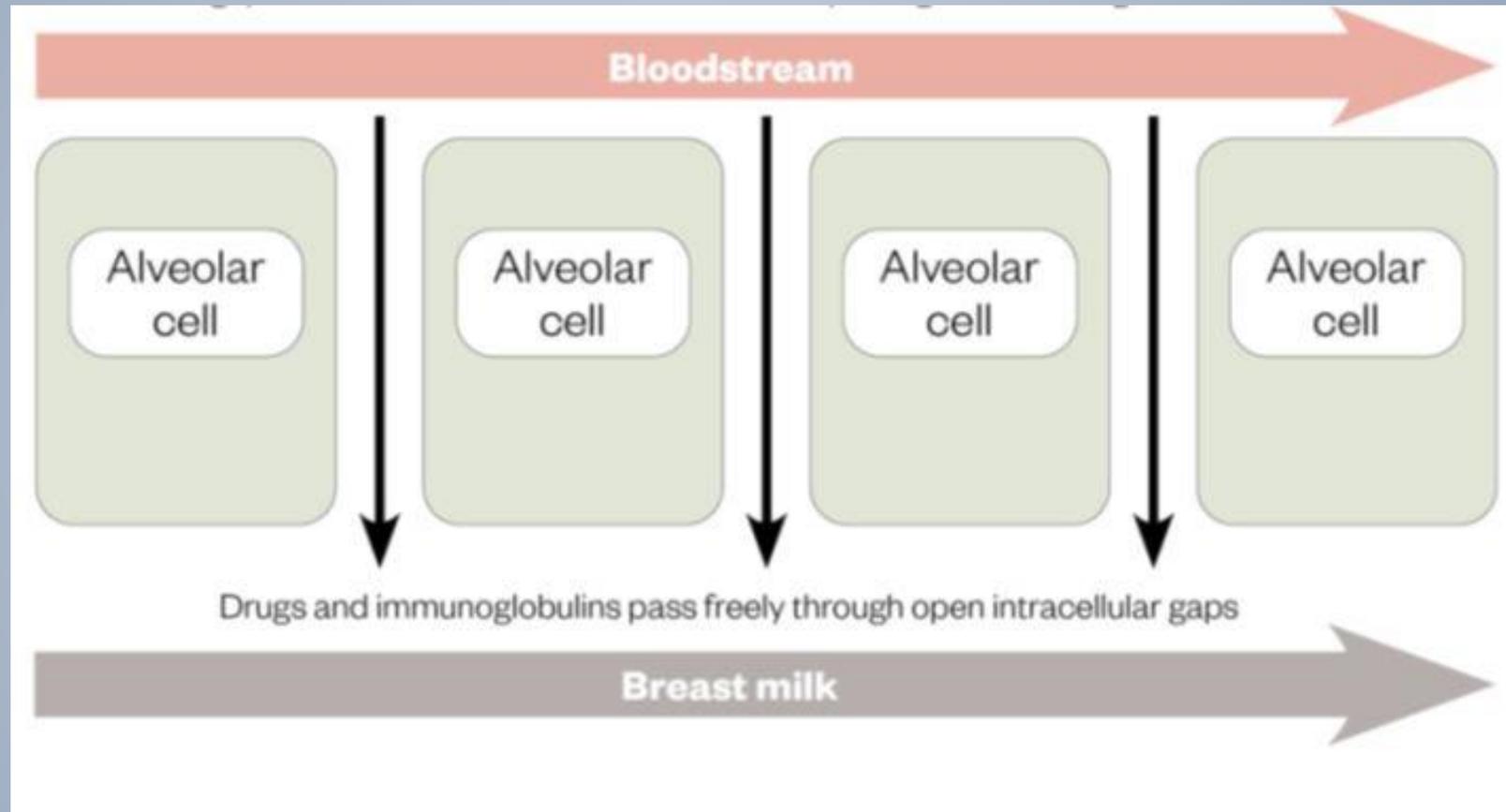
<https://www.youtube.com/watch?v=tS4wkZ2UNUs&t=17s>

Which drugs to choose where possible

- › Anything licensed for children
- › Drugs we have data on
- › Pharmacokinetic data:
 - Poor bio availability
 - Extensive plasma protein binding > 98%
 - Short half life
 - Low milk plasma ratio <1
 - Relative infant dose <10% (only available in specialist texts)

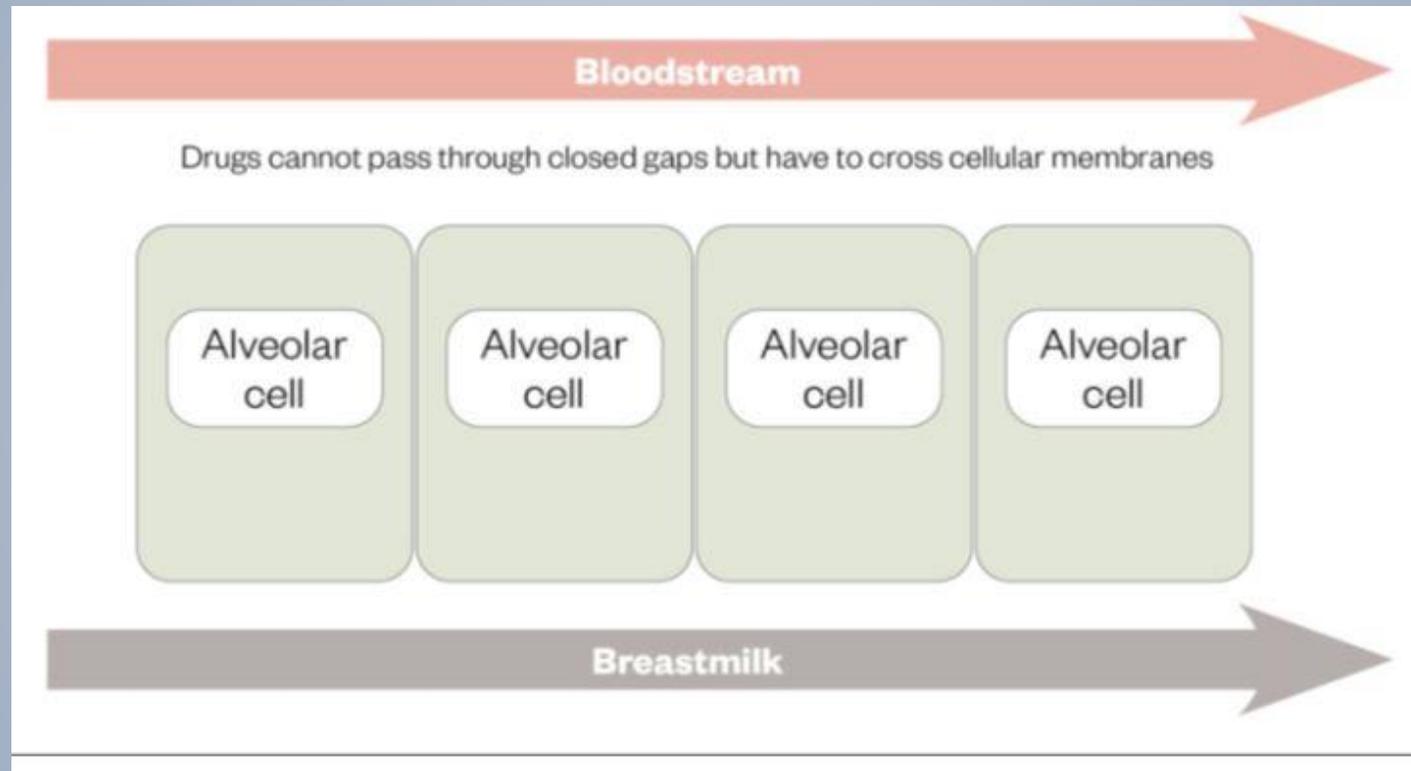


Transfer of drugs in the first few days after birth



The gaps between the cells are wide open to allow the passage of immunoglobulins which are large molecules. This allows free passage of all medication BUT this is when we give most drugs to breastfeeding women with least concern.

Transfer after the first few days after birth

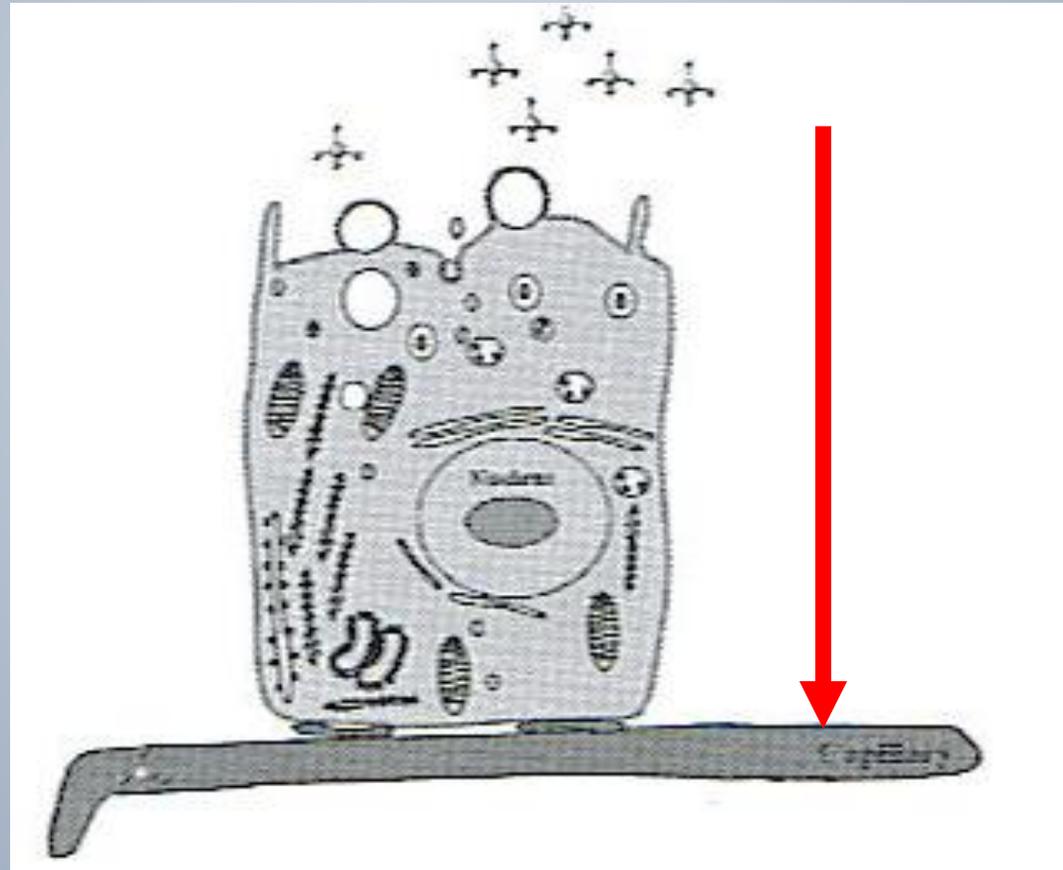


After the first few days the gaps between the cells close and prevent the passage of large molecules further. Drugs now have to pass across the cell membranes



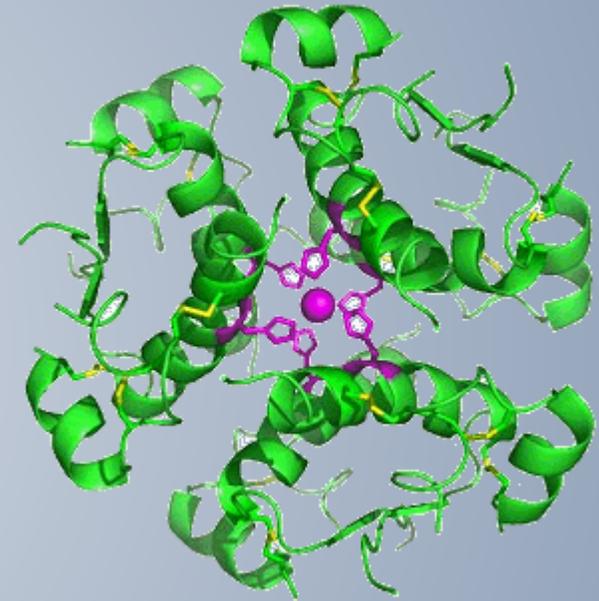
How do drugs get into breastmilk

“Simple” diffusion - 99% drugs pass this way and have to cross the cell membranes to get into milk



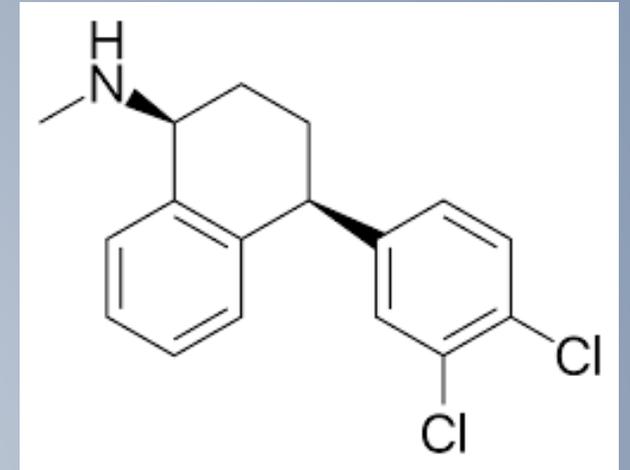
Oral bioavailability

- › Drugs with poor oral bioavailability are large molecules which cannot pass through cell membranes
- › They are usually drugs given ONLY by injection/infusion
- › If a drug can't get be absorbed from the gut however much is in milk, baby can't absorb it e.g. gentamycin, teicoplanin, meropenem

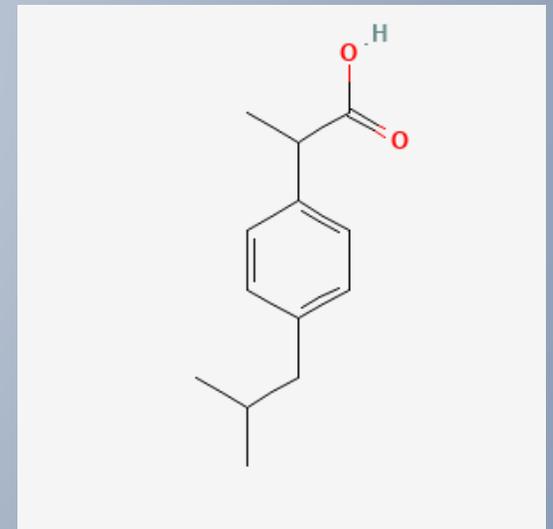


Plasma Protein Binding

- › Drugs which are highly bound to proteins in the maternal plasma are unable to transfer into breastmilk in high levels
- › Ideal drug for breastfeeding mother is highly protein bound >90%
- › Data is only available in specialized texts



Sertraline 98%



Ibuprofen >99%

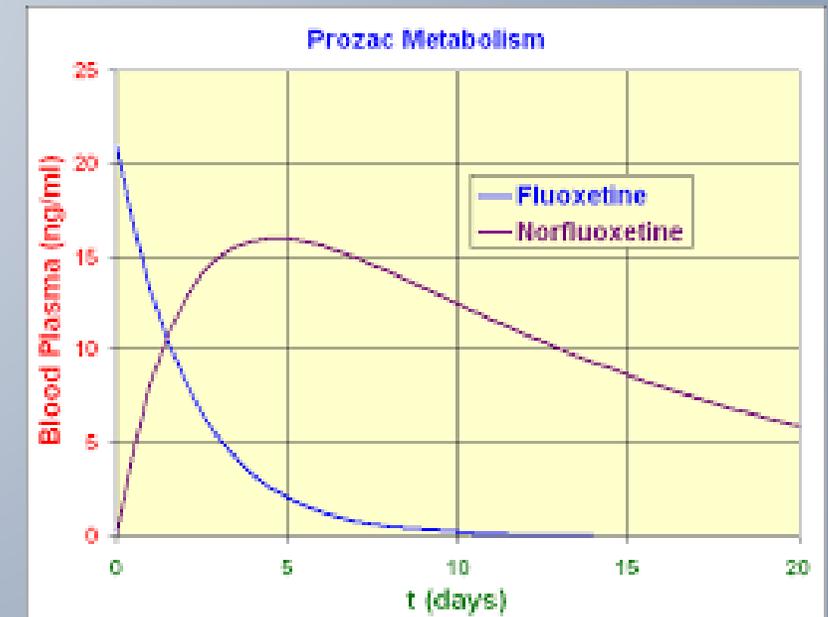
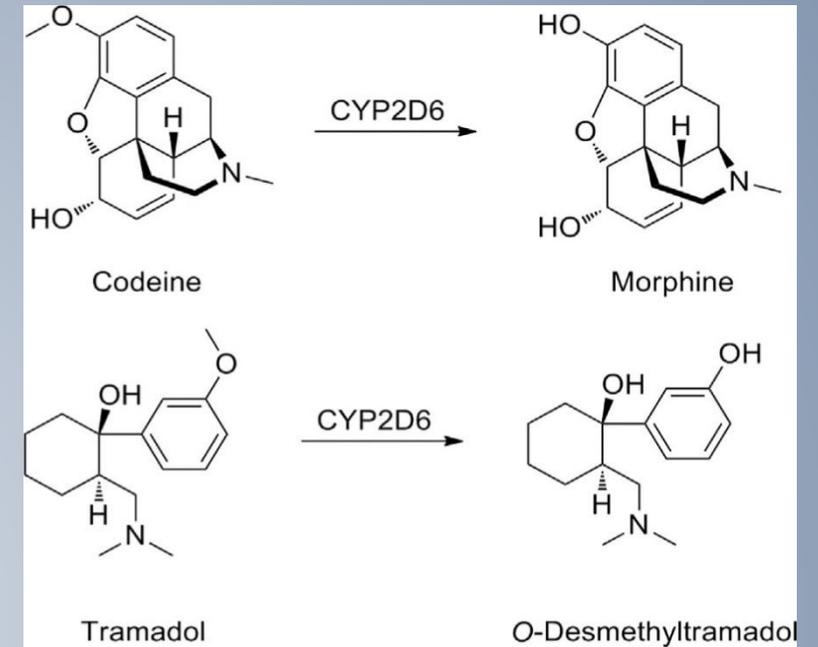
Milk Plasma Ratio

- › the higher the M/P ratio, the more drug is found in breastmilk
- › The M/P is the ratio of the amount of drug in the maternal plasma and the amount of drug in milk
- › For breastfeeding mothers we choose drugs with MP ratio <1
- › M/P ratios above 1 suggest that the drug concentrates in breastmilk e.g. iodine up to 26, cannabis 8, alcohol 1
- › As the level in the mother's blood falls the drug is pulled back from breastmilk, it is not stuck in milk



Active metabolites

- › Some metabolites may have longer half-lives than the original drug and so can extend levels in milk making them less suitable for lactating mothers
- › E.g. Fluoxetine half-life 2-3 days . Norfluoxetine 360 hours (15 days)
- › Codeine and Tramadol CYP2D6 influence





Relative Infant dose

- › Widely being recognised as gold standard
- › RID < 10% compatible
- › First introduced by Bennet 1996
- › Widely used by Hale

Relative Infant Dose

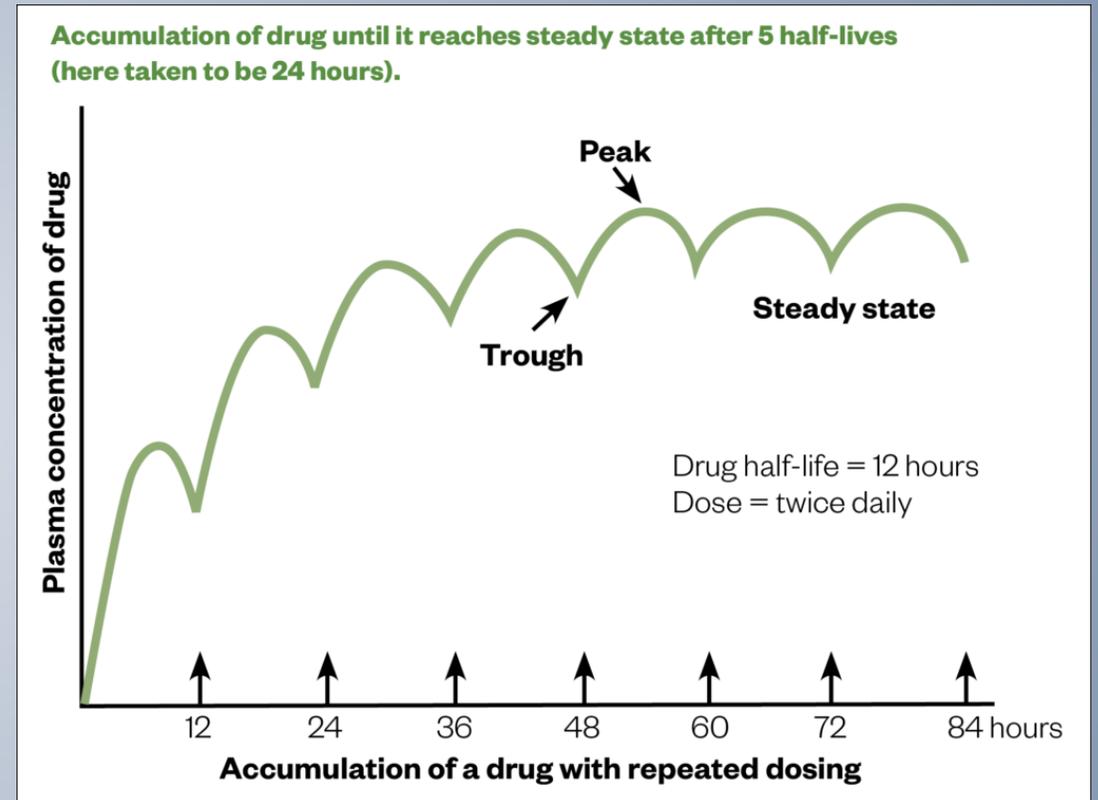
$$\text{RID} = \frac{\text{Dose.infant} \left(\frac{\text{mg}}{\text{kg}} \right) / \text{day}}{\text{Dose.mother} \left(\frac{\text{mg}}{\text{kg}} \right) / \text{day}}$$

Dose.infant = dose in infant/day

Dose.mother = dose in mother/day

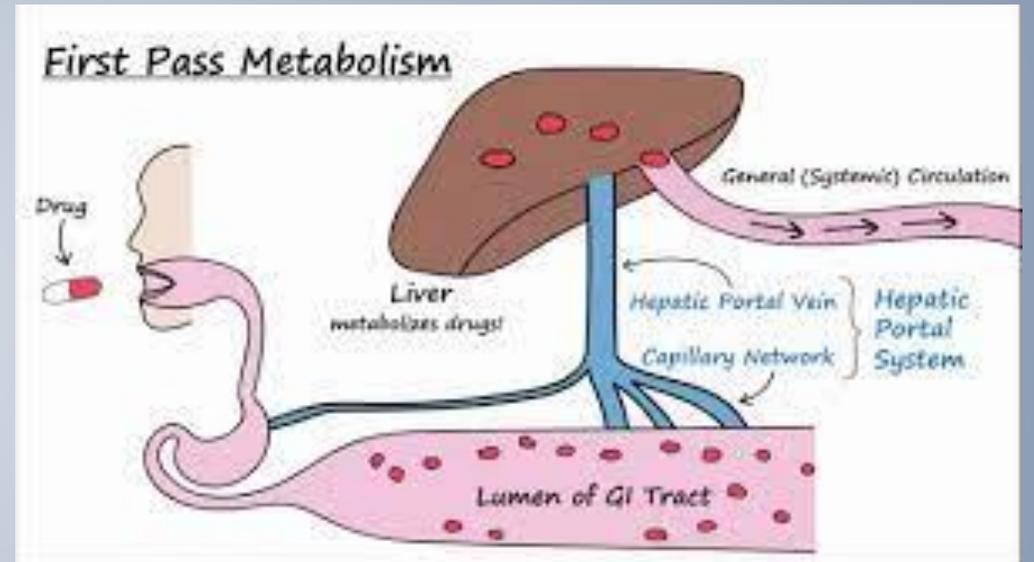
Timing of drugs and feeds

- › The time to maximum level in breastmilk is often quoted
- › Mums try desperately to time feeds with drug levels at their lowest
- › BUT ... once any drug has been taken for 3 days (or 5 half lives) reaches steady state so timing is pointless



First pass metabolism

- › The drug is absorbed from the GI tract and passes via the portal vein into the liver where it may be metabolized.
- › This means that less drug is available to pass into the blood stream E.g. morphine



First do no harm?

- › No breastfeeding mother should be asked to choose between breastfeeding and a dental procedure involving medication
- › Need to use evidence based information rather than just the BNF which is still currently based largely on the SPC of manufacturers although it is changing
- › Telling a mother to interrupt breastfeeding may put her at risk of mastitis and may cause difficulties for the baby who hasn't ever taken milk from a bottle
- › Breastfeeding isn't just about food





Are dental practitioners well informed about breastfeeding ?

- › In a study in Romania in 2019 more than half of the practitioners surveyed would treat a breastfeeding woman in any emergency situations, only if she postpone breastfeeding for the next 24 hours. About 85% of the respondents will perform the anaesthesia in a nursing woman, but about just 1/3 will use mepivacaine and less than 3% will use lidocaine.
- › The authors concluded that post-graduate courses are required to update the knowledge of dentists in this domain.
- › Aranka, Ilea & Lazar, Adela & Boşca, Adina & Bordea, Roxana & Mirica, Codruta & Ionel, Anca & Campian, Radu & Petrescu, Nausica & Băbţan, Anida & Sovrea, Alina. (2019). Assessment of Dentists' Knowledge Concerning the Management of Breastfeeding Patients in Dental Office. 15. 1-7. 10.26717/BJSTR.2019.15.002736. <https://biomedres.us/fulltexts/BJSTR.MS.ID.002736.php>

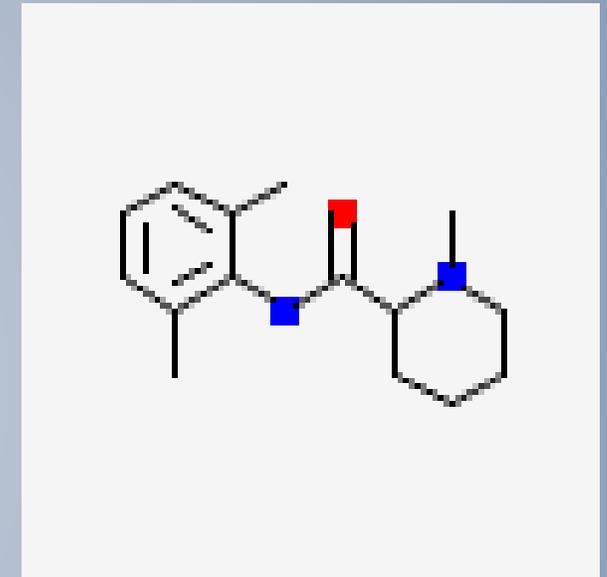


Could local anaesthesia while breast-feeding be harmful to infants?

- › This study suggests that even if a nursing mother undergoes dental treatment with local anaesthesia using lidocaine she can safely continue breastfeeding.
- › Plasma Protein Binding 70%, oral bioavailability <35%. RID <3.1% ([Hale Medications and Mother's Milk 2021](#))
- › Levels as a local anaesthetic are low and the lidocaine is poorly absorbed by the infant. Lidocaine is not expected to cause any adverse effects in breastfed infants. No special precautions are required (LactMed.www.ncbi.nlm.nih.gov/books/NBK501230/).
- › [Giuliani M, Grossi GB, Pileri M, Lajolo C, Casparrini G. Could local anesthesia while breast-feeding be harmful to infants? J Pediatr Gastroenterol Nutr. 2001 Feb;32\(2\):142-4](#)

Mepivacaine

- › Plasma Protein Binding 60-85%, oral bioavailability 55%. Half life < 3.2 hours
- › No data are available on the transfer of mepivacaine into human milk; however, its structure is practically identical to bupivacaine and one would expect its entry into human milk is similar and low.
- › <https://www.ncbi.nlm.nih.gov/books/NBK501607/>



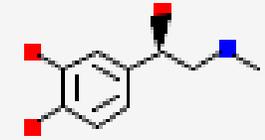
Articaine

- › No data are available on its use in breastfeeding mothers. As with lidocaine, however, its transfer into human milk is probably minimal. If ingested, it would be rapidly hydrolysed by gastric esterases.
- › Half life 1.8 hours, plasma protein binding 60-80%.
- › <https://www.ncbi.nlm.nih.gov/books/NBK501746/>
- › So why does the BNF say avoid breastfeeding for 48 hours as it will all be gone from maternal system in 9 hours and destroyed in the gut? Because the manufacturers are not required to take responsibility when compiling SPC.



Adrenaline/epinephrine

- › Often added to local anaesthetic agents
- › it is almost instantly destroyed in the gastrointestinal tract. It is unlikely that any would be absorbed by the infant
- › T $\frac{1}{2}$ 2 minute and poor oral bioavailability
- › No information is available on the use of epinephrine during breastfeeding. Because of its poor oral bioavailability and short half-life, any epinephrine in milk is unlikely to affect the infant www.ncbi.nlm.nih.gov/books/NBK501642/



Pain relief

- › Paracetamol
- › NSAID: Ibuprofen, diclofenac or naproxen
- › Short term use of opioid all compatible with normal breastfeeding : opioid of preference is dihydrocodeine as the oral bio availability is 20% due to substantial first pass metabolism.
- › MHRA recommendation codeine should not be used during breastfeeding. Maternal metabolism can vary – may be ineffective, effective, produce adverse events in mother and baby





Antibiotics

- › The antibiotics:
- › amoxicillin,
- › Metronidazole
- › Macrolides
- › cephalosporins

are all compatible with normal breastfeeding

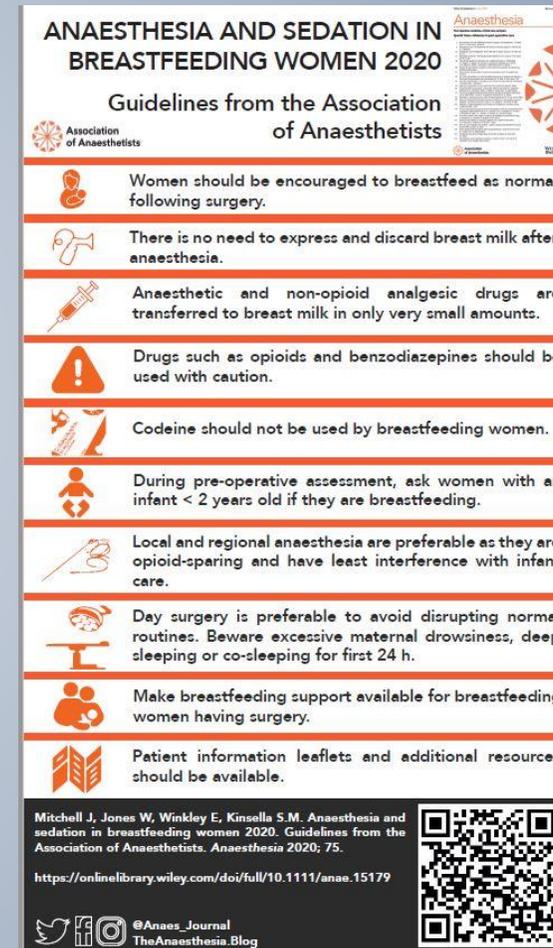
<https://breastfeeding-and-medication.co.uk/fact-sheet/antibiotics-and-breastfeeding>

Compatibility of antibiotics during lactation		
Penicillins		
penicillin V, amoxicillin, co-amoxiclav, cloxacillin, flucloxacillin		licensed for use in children
Cephalosporins		
cefadroxil, cefalexin, cefuroxime, ceftriaxone, cefepime		licensed for use in children
Macrolides		
erythromycin, azithromycin, clindamycin, clarithromycin		Observe for pyloric stenosis in neonates but current evidence is that the risk is low.
Aminoglycosides		
Gentamicin:	oral bioavailability <1%	will only pass into milk in first few days
Vancomycin	oral bioavailability negligible	will only pass into milk in first few days
Teicoplanin	no studies but oral bioavailability low	licensed for use in children
Quinolones		
Ofloxacin	plasma protein binding 32%, oral bio availability 98%, relative infant dose 3.1%	Avoid if possible because studies limited
Levofloxacin	enantiomer of ofloxacin, relative infant dose 10.5% - 17.2%	Avoid if possible.
Moxifloxacin	no studies	Avoid if possible
Norfloxacin	no studies	Avoid if possible
Eprofloxacin	plasma protein binding 40%, oral bio availability 50-85%, relative infant dose 0.44% - 6.34%	Given directly to young rats causes a type of juvenile arthritis but not seen in the amount passing through breastmilk. Chelated by calcium in milk. Avoiding breastfeeding for 3 to 4 hours after a dose. Use only if no other antibiotic is suitable
Tetracyclines		
		compatible with breastfeeding in courses < 3 weeks as chelated by calcium in milk, avoid long term use
Doxycycline		
Tetracycline, tetracycline, oxytetracycline		avoid long term use
Other antibiotics		
Trimethoprim	relative infant dose 3.9-9%	Licensed for paediatric use.
Nitrofurantoin		Licensed for paediatric use. Use with care in G6PD deficient infants (rare).
Metronidazole	plasma protein binding <20%, oral bio availability complete, relative infant dose 12.6-13.5%	Studies show no untoward effects at a dose of 200-400mg three times a day. Said to alter taste of milk
Meropenem	oral bioavailability nil	will only pass into milk in first few days

Dental sedation and breastfeeding

- › The use of midazolam during breastfeeding is included in the anaesthesia guidelines <https://associationofanaesthetists-publications.onlinelibrary.wiley.com/doi/full/10.1111/anae.15179>

Breastfeeding can continue as normal



ANAESTHESIA AND SEDATION IN BREASTFEEDING WOMEN 2020
Guidelines from the Association of Anaesthetists

Association of Anaesthetists

-  Women should be encouraged to breastfeed as normal following surgery.
-  There is no need to express and discard breast milk after anaesthesia.
-  Anaesthetic and non-opioid analgesic drugs are transferred to breast milk in only very small amounts.
-  Drugs such as opioids and benzodiazepines should be used with caution.
-  Codeine should not be used by breastfeeding women.
-  During pre-operative assessment, ask women with an infant < 2 years old if they are breastfeeding.
-  Local and regional anaesthesia are preferable as they are opioid-sparing and have least interference with infant care.
-  Day surgery is preferable to avoid disrupting normal routines. Beware excessive maternal drowsiness, deep sleeping or co-sleeping for first 24 h.
-  Make breastfeeding support available for breastfeeding women having surgery.
-  Patient information leaflets and additional resources should be available.

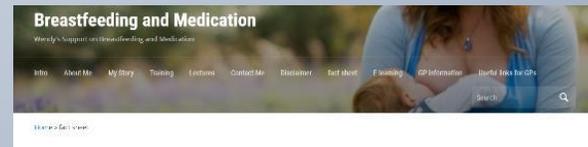
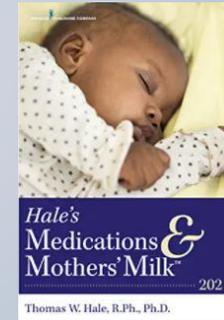
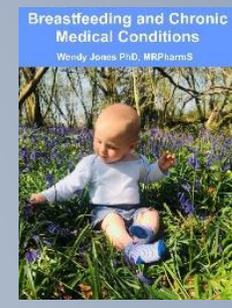
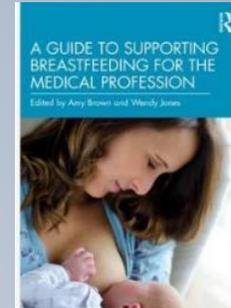
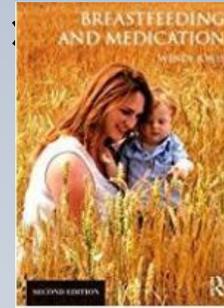
Mitchell J, Jones W, Winkley E, Kinsella S.M. Anaesthesia and sedation in breastfeeding women 2020. Guidelines from the Association of Anaesthetists. *Anaesthesia* 2020; 75.
<https://onlinelibrary.wiley.com/doi/full/10.1111/anae.15179>

 @Anaes_Journal
TheAnaesthesia.Blog



Resources

- › LactMed - <https://www.ncbi.nlm.nih.gov/books/NBK501922/>
- › UKDILAS - <https://www.sps.nhs.uk/home/guidance/safety-in-breastfeeding/>
- › Hale – Medications and Mothers Milk - <https://www.halesmeds.com/>
- › BfN Factsheets www.breastfeedingnetwork.org.uk/drugs-factsheets/
- › Breastfeeding and Medication <https://breastfeeding-and-medication.co.uk/fact-sheet/list-of-factsheets-available-on-breastfeeding-and-medication>



Healthcare professionals need to use evidence based sources to check the safety of drugs in breastmilk and be sensitive to the needs of mothers around infant feeding.

Contact details

wendy@breastfeeding-and-medication.co.uk

www.facebook.com/breastfeedingandmedication

