



ST. JAMES'S HOSPITAL • DUBLIN 8







TEL 01-4730589 or 1850-727-727 • FAX 01-4730596

E-Mail: nmic@stjames.ie

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DRUGS IN LACTATION

SUMMARY

-  **Breastfeeding is the optimal method of infant feeding, and has numerous physical and psychological benefits for both infant and mother**
-  **Most drugs taken by the nursing mother are excreted into breast milk**
-  **Drug, infant, and maternal factors all influence the safety of drug use during lactation**
-  **Risks to the infant during maternal drug therapy may be minimised by careful selection of drug, dose, route, and timing of administration relative to feeding**
-  **Cessation of breastfeeding during drug therapy is rarely necessary**
-  **A small number of drugs are contraindicated during lactation**

INTRODUCTION

Breastfeeding is the best method of feeding infants and is regarded as one of the most important measures to improve child health. Not only is breast milk nutritionally optimal in terms of content and quantity, breastfeeding also provides other physical and psychological benefits to both infant and mother.^{1,2,3,4} Exclusive breastfeeding for the first six months of life is recommended by the World Health Organisation.⁵ It is inevitable that during the breastfeeding period some mothers will need drug treatment. Almost any drug taken by a nursing mother will be excreted into breast milk, and therefore the effects of maternal drug ingestion on the nursing infant must be considered.^{3,6} Fortunately, most drugs only appear in very small amounts in breast milk, and few drugs are contraindicated during lactation.^{2,7} (Table 2)

When prescribing for a lactating mother, consideration must be given to the risks and benefits of drug therapy, to the mother as well as to the infant.^{1,8} The amount of drug excreted into breast milk, and the potential to cause adverse effects in the infant vary considerably, and are dependent upon drug factors, infant factors and maternal factors. It is usually possible to minimise risks by careful selection of drug, dose, route and timing of administration relative to feeding.^{9,10} (Table 1) Sometimes the mother's health requires the use of medications that are too toxic for breastfeeding to continue safely (e.g. antineoplastic agents). In such cases it is in the best interests of the mother and infant for breastfeeding to be discontinued.⁹

Few studies have been undertaken on the effects of maternal drug therapy on breastfed infants. Evidence for safety or harm is primarily based on case reports, clinical experience and anecdotal reports.⁷ The limitations of the available data should be borne in mind when considering drug therapy in a breastfeeding mother.

FACTORS THAT INFLUENCE THE SAFETY OF DRUG USE DURING LACTATION

Drug factors (1) *Diffusion or active transport* - Drugs enter milk primarily by diffusion, i.e. as the mother's plasma drug level rises, the concentration in milk rises. This also means that most drugs will exit the milk as the maternal plasma concentration falls.² In a few instances drugs are transferred into milk by active transport mechanisms, resulting in greater concentrations of drug in milk than in maternal plasma.^{6,9} (2) *Protein binding* - Drugs which are highly protein bound in the maternal plasma (e.g. warfarin) achieve lower breast milk levels.^{1,2,11} (3) *Lipid-solubility* - Highly lipid-soluble drugs penetrate milk in higher concentrations.² (4) *Degree of ionisation* - Drugs which are unionised in plasma are excreted into milk in greater amounts than ionised compounds.⁹ (5) *Molecular weight* - Drugs with a low molecular weight (e.g. lithium salts) appear in breast milk very rapidly after maternal ingestion, whereas drugs with a high molecular weight (e.g. heparin) do not enter milk.^{1,11} (6) *Oral bioavailability* - Some drugs are destroyed in the infant's gut, and therefore do not pass into the systemic circulation and thus pose no risk.¹ Other drugs are only poorly absorbed from the GI tract (e.g. aminoglycosides), and thus it is unlikely that the infant will absorb significant quantities.² (7) *Half-life* - Exposure to drugs with long half-lives or active metabolites may be prolonged, and risk of adverse effects therefore increased. In general such agents should be avoided, particularly in premature or newborn infants where immature excretory functions may further prolong exposure.¹ (8) *Non-dose-related toxicity* - A few drugs may cause idiosyncratic or allergic reactions unrelated to the amount ingested.¹

Infant factors (1) *Age* - Neonates (and particularly premature infants) are at greater risk from exposure to drugs via breast milk, because of immature excretory functions and the consequent risk of drug accumulation. In addition, older infants will ingest decreasing amounts of drug as they are weaned from breast milk onto solid foods.¹ (2) *Health status* - Prematurity, low birth weight or illness put infants at higher risk of adverse drug effects. If possible, exposure to drugs in breast milk should be avoided in such infants. Additional risk factors include renal or liver impairment, glucose-6-phosphate dehydrogenase (G6PD) deficiency or dehydration.⁷

Maternal factors (1) *Dose* - In general there is a direct relationship between maternal dose and milk levels. Dose frequency will affect the ability to time breastfeeding to avoid maximum concentrations in milk.¹ (2) *Route of administration* - Parenteral administration normally produces higher maternal plasma levels than oral administration, while drugs administered topically or by inhalation normally produce very low systemic levels.¹ (3) *Health status* - Maternal drug accumulation due to renal or hepatic impairment may increase the hazard to the infant¹

Table 1: General principles of prescribing in lactation^{1,2,7,8,9,10,11}

- Consider whether drug therapy is necessary, or if it can be delayed until weaning
- It is preferable to use a drug which is licensed or acceptable for use in infants
- Avoid drugs known to cause serious toxicity in adults or children
- Avoid new drugs, for which little data are available, where there is an older, more established alternative which has been used during breastfeeding without apparent harm to infants
- Within a drug class, choose one that passes poorly into milk (based on the physicochemical properties of the drug and published data) and has no active metabolites. If possible, avoid drugs (or their active metabolites) that have long paediatric half-lives, as these may accumulate in the infant
- Monotherapy is preferable to multiple drug regimens, which may have additive adverse effects
- Choose a route of administration which minimises maternal drug levels, e.g. topical/local rather than systemic
- Any drug should be used at the lowest effective dose and for the shortest time
- If the drug has an appropriately short half-life the risk of drug effects in the infant may be minimised by dosing after breastfeeding. This strategy may not work in the case of a newborn infant who nurses more frequently

- Long-acting formulations of drugs likely to cause serious side-effects are best avoided as it is difficult to time feeds to avoid significant amounts of drug in breast milk
- Cessation of breastfeeding may be necessary for some medications
- Monitor the infant for adverse effects. In some cases it may also be necessary to monitor infant's plasma level of a drug
- Counsel mothers to seek advice before using over-the-counter medications

SELECTED DRUGS IN LACTATION

Many drugs are not licensed for use during lactation. This publication does not address whether each of the following drugs is licensed or not for use during lactation. Consult the manufacturer's Summary of Product Characteristics (SPC) for licence status.

Non-inclusion of a drug in this section does not imply safety.

Anti-infectives Penicillins and cephalosporins appear in low concentrations in milk and have not been associated with adverse effects in infants. There is however a potential for direct effects on the infant (e.g. allergy or sensitisation), for modification of the bowel flora, and for interference with the interpretation of culture results in the infant.^{1,3,9,10} They are considered to be safe for use in lactation.^{1,3,6,12} Erythromycin is concentrated in breast milk, but has not been associated with adverse effects, and is considered to be compatible with breastfeeding.^{1,3,12} However, the same potential concerns apply as with penicillins. There are no studies on the use of clarithromycin in breastfeeding and it should only be used with caution.³ Trimethoprim is considered to pose negligible risk to breastfed infants, and is safe to use in breastfeeding.^{1,3,12} Exposure to sulphonamides through breast milk apparently does not pose a significant risk to healthy, full-term infants.^{3,6} Sulphonamides should be avoided if the infant is ill, stressed, premature or has hyperbilirubinaemia.³ They may increase the risk of bilirubin encephalopathy in jaundiced neonates, by competing for protein binding sites with bilirubin. They are also contraindicated if the infant has G6PD deficiency, due to the risk of haemolysis.^{6,9} Metronidazole is probably safe in lactation.^{1,3,6,12} Large single doses should if possible be avoided,¹ but if used, breastfeeding should be withheld until 12 to 24 hours after a single 2g dose.^{2,3} Metronidazole in breast milk may taste unpleasant, but consequent feeding problems do not usually occur.¹ Ciprofloxacin is contraindicated in breastfeeding, due to the potential for arthropathy (based on animal data) and other serious toxicities. Breastfeeding should be temporarily suspended during treatment and resumed 48 hours after the last dose.^{3,6}

Aciclovir is not thought to be harmful in lactation, and no adverse effects have been reported.^{1,3,6,12} In addition, it is a drug which has been safely used therapeutically in infants.^{6,10}

The topical imidazoles, e.g. ketoconazole, miconazole and clotrimazole, are compatible with breastfeeding.^{1,2,13}

Of the anthelmintics, mebendazole is safe for use in breastfeeding, as the amounts of drug excreted into milk are below the level of detection and appear to be clinically insignificant.³

Analgesics and Non-steroidal anti-inflammatory drugs (NSAIDs) These medications are some of the most frequently prescribed for the lactating mother, especially during the early postpartum period. As with any medication, a brief period of therapy may differ from chronic exposure.¹⁰

Paracetamol is considered to be the safest analgesic to use in lactation.^{1,6,12,14} Codeine analgesics are commonly used postpartum; side effects in infants are extremely rare and seldom reported. Rare cases of neonatal apnoea have been reported, but at higher doses. Premature or weakened infants should be observed for sedation and apnoea. The amount of codeine excreted into breast milk is low and it is generally considered to be a safe analgesic to use.^{1,2,3,6,12,14}

There is no consensus on the use of aspirin during lactation - some sources state that it may be used with caution, others that it should be avoided due to the potential for accumulation in the infant, which theoretically may result in Reye's syndrome and platelet dysfunction.^{6,7,14} Low dose aspirin used for thromboprophylaxis is probably safe, although the infant should be observed for adverse effects.^{6,14} Diclofenac, ibuprofen and mefenamic acid are all

compatible with breastfeeding, as they only appear in very low concentrations in milk.⁶ However, due to its adverse effect profile, there are safer alternatives to mefenamic acid.^{3,14} Due to one reported case of seizure in an infant exposed to indomethacin, it is generally considered to be contraindicated in breastfeeding.^{1,15}

There is no information available on the COX-2 inhibitors celecoxib and rofecoxib in lactation, and they should therefore be avoided.

Antidepressants There is limited information on use of the selective serotonin reuptake inhibitors (SSRIs) in lactation, including any potential long-term adverse effects. They should be used with caution.³ Sertraline or paroxetine are preferred to fluoxetine.^{1,16} Fluoxetine appears in relatively greater amounts in milk, and has a highly active metabolite. Fluoxetine and its metabolite norfluoxetine both have very long half-lives, which may result in accumulation in the infant.^{1,2,16} Adverse effects have been reported in some infants following exposure to fluoxetine in breast milk.^{1,3} There have been case reports of adverse effects with citalopram, but other infants have had no adverse effects, and plasma levels that were very low or absent.^{3,16,17}

Tricyclic antidepressants (TCAs) should be used with caution in breastfeeding women. Infants should be monitored for sedation or irritability.¹ Doxepin is contraindicated in lactation, as its active metabolite may accumulate in the infant, and there has been a case reported of respiratory depression and sedation in one infant.^{1,3,18}

Nefazodone, reboxetine, venlafaxine, and monoamine oxidase inhibitors should all be avoided in lactation, due to lack of published data.^{1,19} In studies in a limited number of patients, moclobemide has been detected in only small amounts in breast milk, thus the benefits of drug therapy should be weighed against possible risks to the infant.^{20,21,22}

In summary, TCAs (except doxepin) and SSRIs are considered to be compatible with breastfeeding, but careful monitoring of the infant is essential when any antidepressant is used.^{9,23,24,25,26}

Hormonal contraceptives Although full breastfeeding provides a period of infertility, eventually this protection wanes.²⁷ During lactation non-hormonal methods of contraception should be used if possible.¹ The progestogen-only pill (POP) is the preferred method of hormonal contraception, as it does not adversely affect milk volume or composition.^{1,3,27,28}

The amount of drug transferred to the milk is minute, and unlikely to present any hazard. The contraceptive combination of full lactation plus the POP is highly effective.²⁹ Most studies of the injectable contraceptive medroxyprogesterone acetate show either no change, or an improvement, in the quantity of milk produced and duration of lactation.^{29,30} It appears in breast milk in very small quantities, and no morbidity or long-term effects on infant growth and development have been reported.^{2,29} Combined oral contraceptives are not recommended, as they shorten the duration of lactation, decrease milk production, and decrease the protein and nitrogen content of the milk.^{3,29}

Table 2: Some drugs which are contraindicated during breastfeeding^{1,3,6,7,8,31}

Amiodarone	Iodides
Antineoplastic agents	Indomethacin
Chloramphenicol (IV/oral)	Lithium
Ciprofloxacin	Oestrogens (high dose)
Doxepin	Pethidine (multiple doses)
Ergotamine	Radioactive isotopes
Gold salts	Vitamin D (high dose)

References available on request.

Every effort has been made to ensure that this information is correct and is prepared from the best available resources at our disposal at the time of issue. Prescribers are recommended to refer to the drug data sheet or summary of product characteristics (SPC) for specific information on drug use.

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