World Journal of Biology Pharmacy and Health Sciences
eISSN: 2582-5542
Cross Ref DOI: 10.30574/wjbphs
Journal homepage: https://wjbphs.com/

(REVIEW ARTICLE)

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A systematic review article on anaesthesia and analgesia drug effects on Breast milk composition and lactation

Shubha Srinivasareddy *

Assistant Professor, Penn state Health. PA, USA.

World Journal of Biology Pharmacy and Health Sciences, 2024, 18(03), 043–052

Publication history: Received on 11 April 2024; revised on 27 May 2024; accepted on 30 May 2024

Article DOI: https://doi.org/10.30574/wjbphs.2024.18.3.0299

Abstract

Breastfeeding is one of the most important aspects of maternal and child health. It is important to understand how medications affect breast milk and lactation for mothers. The absolute dose transferred during the colostrum period is still very low; the total intake is generally less than 30–100 mL/day for the first few days postpartum. This review article presents evidence-based guidelines for pain management and anaesthesia in breastfeeding women. Various pharmacological factors determine the transmission of a drug into breast milk and its effect on the baby: the plasma protein binding, molecular weight, volume of distribution, pKA, lipid solubility, and maternal pharmacogenomics. This article synthesises perspectives on the safety of medications in situations where there is insufficient data to conclusively support ongoing breast feeding without the requirement to express and discard breast milk after undergoing anaesthesia. The article also includes the potential transfer of various pain medicines, such as NSAIDs and opioids like morphine, methadone, and remifentanil, through breast milk and their impact on the new-born. However, it is important to exercise caution while using medications due to the potential risks they pose to infants. The paper highlights the significance of professional collaboration in addressing anaesthesia issues during pregnancy and the postpartum period for parturient women. The article also examines the effects of immunosuppressants on women who have undergone transplants, emphasising the importance of careful surveillance and individualised care to safeguard the health of both the mother and the infant.

Keywords: Anaesthesia; Analgesia; Breastfeeding; Intensive Care Unit (ICU); Lactation

1. Introduction

Breastfeeding is the best option for new-borns, according to all research studies. Numerous studies have confirmed the clear advantages it offers in terms of infant growth and development. However, the topic of taking medication while breastfeeding remains highly debated. Due to a lack of understanding among many clinicians regarding the effects of drugs on breast milk, a large number of women opt to discontinue breastfeeding in order to take medication. Given the significant number of infants being prescribed medication during their early stages, it is not surprising that one of the most frequently asked questions in paediatrics relates to the compatibility of different drugs with breastfeeding. Sadly, the majority of healthcare professionals focus mainly on the information provided in the package inserts or discourages breastfeeding without thoroughly examining the literature on medication for accurate guidance [1].

An in-depth literature review is done to fully understand the wide range of effects that medications have on lactating women in the ICU, HDU or other units in the hospital. This knowledge is very important for giving critically ill patients specialised hospital care. This review is important for healthcare professionals to fully understand how anaesthesia, analgesia, and breastfeeding affect each other and how these medicines are absorbed, distributed, metabolised, and eliminated in the breast milk. Realising and understanding how complicated these problems are is important for helping

* Corresponding author: Shubha Srinivasareddy

our lactating mothers in every way, meeting all of their mental and physical needs so they can get better care for themselves and their babies [1], [2].

1.1. Importance of Drug Transfer Studies

In the last 25 years, researchers continue to know more now than ever before about the use of breastfeeding. It is generally accepted that all medications transfer into human milk to some degree, although almost always quite low. Only rarely does the amount transferred into milk produce clinically relevant doses for the infant. However, once medications transfer into human milk, other kinetic factors are involved. One of the most important factors is the oral bioavailability of the medication to the infant. Numerous medications are either destroyed in the infant's gut, fail to be absorbed through the gut wall, or are rapidly picked up by the liver. Once in the liver, they are either metabolized or stored, but often never reach the mother's plasma [3].

Drugs normally enter milk by passive diffusion, driven by equilibrium forces between the maternal plasma compartment and maternal milk compartment [1]. Drugs pass from maternal plasma through capillaries into lactocytes lining the alveolus. Medications must generally pass through both bilayer lipid membranes of alveolar cells to penetrate milk; although early on medications may pass between alveolar cells (first 72 hours postpartum). During the first three days of life, large gaps between alveolar cells exist. These gaps permit enhanced access to milk for most drugs, many immunoglobulins, maternal living cells (lymphocytes, leukocytes, macrophages), and other material proteins. By the end of the first week, alveolar gaps swell under the influence of prolactin, subsequently closing intracellular spaces, reducing transcellular entry of most maternal drugs, proteins, and other substances into the milk compartment. It is generally agreed that medications penetrate into milk more during the colostrum period than mature milk [4]. However, the absolute dose transferred during the colostrum period is still low; the total volume is generally less than 30–100 mL/day for the first few days postpartum[1], [5].

In most instances, the most important determinant of drug penetration into milk is the mother's plasma level. Almost without exception, as the level of medication in the mother's plasma rises, the concentration in milk increases as well. Drugs enter and exit milk as a function of the mother's plasma level. As soon as the maternal plasma level of medication begins to fall, equilibrium forces drive medication out of the milk compartment back into maternal plasma for elimination. In some instances, drugs are trapped in milk (ion trapping) due to lower pH [6].

Medicines with a high pKa are affected by the lower pH of human milk (7.2), which causes weekly basic medicines, such as barbiturates, to change their ionic state and cease re-entering the mother's bloodstream. Researchers refer to this process as ion trapping. Particular chemicals are actively pumped into milk by cellular pumping mechanisms. The most famous is the iodine pump, which functions similarly to the thyroid gland's pump. Its goal is to guarantee that the baby gets enough iodine to produce enough thyroxine. Iodine-131 and other radioactive iodides should be avoided since there is an increase in milk due to the iodine pump and can reach extremely high amounts. The degree of protein binding and lipid solubility are two physicochemical variables that are significant when evaluating medicines in lactating moms [7].

Drugs that are highly lipid-soluble tend to penetrate into milk in higher concentrations. CNS-active drugs, which have unique characteristics that allow them to enter milk, can be expected to have higher levels in milk, although the amounts are often subclinical. Many neuroactive drugs produce Relative Infant Doses of more than 5%. Protein binding also plays a significant role. Drugs circulate in maternal plasma either bound to albumin or freely soluble in plasma. It is the free component (unbound fraction) that transfers into milk, while the bound fraction remains in the maternal circulation. Therefore, a drug with high maternal protein binding, like warfarin and many NSAIDs, will have reduced milk levels because they are excluded from the milk compartment [8], [9].

Some drugs are poorly stable in infant gut due to the proteolytic enzymes and acid present in the infant’s stomach. This includes other drugs aside from family omeprazole, and large peptide drugs such as Heparin. The omeprazole family absorbed by infants' gastrointestinal tract does not enter the infant's bloodstream. Thus oral bioavailability is a useful tool to estimate just how much of the drug will be absorbed by infants. Many drugs sequestered in the liver (first pass) may never actually reach the plasma compartment where they are active absorption characteristics such as these ultimately tend to reduce the overall effect of many drugs on breastfed infants. One more popular method of estimating risk is determining Relative Infant Dose (RID). RID is calculated by dividing the infant's dose via milk (mg/kg/day) mother's dose mg/kg/day RID gives clinicians a feeling of just how much medication the infant is exposed to weight-normalized basis.

Relative Infant Dose means,

$$\text{RID} = \frac{Dose\ Infant}{Dose\ Mother}$$

Table 1 Relative Infant Dose (RID) of Anaesthesia Medications and Recommendations

Medication Class	**Mean RID (%)**
Anticholinergics	Unknown: generally considered safe
	with single systemic or ophthalmic dosing
Anticholinesterases	0.1
Antiemetics	Unknown: considered safe due to lack of
	sedating side effects
Benzodiazepines	0
Intravenous Anaesthetics	
- Etomidate	0.1
- Ketamine	Unknown: recommended only if medically necessary
- Propofol	0.1
Local Anaesthetics	0.1
Narcotics	
- Fentanyl	1
- Hydrocodone	3
- Hydromorphone	3
- Morphine	9
- Oxycodone	3 (maximum daily dose 30mg)
- Remifentanil	Unknown: considered safe secondary to short
	half-life
- Codeine/Tramadol	Avoid: FDA warning against use in women with a
	CYP2D6 mutation
Non-narcotic Analgesics	
- Acetaminophen	4 (maximum daily dose < 3gm)
- Ibuprofen	0.5
- Ketorolac	0.3
Miscellaneous	
- Gabapentin	3
- Dexamethasone	Unknown: considered safe (may cause temporary
	loss of milk secondary to decreased prolactin
	levels)
- Diphenhydramine	Unknown: generally considered safe
Volatile Gases	Unknown: considered safe secondary to rapid
	excretion, poor bioavailability and OR scavenging

2. Significance in medical practice, particularly in intensive care units (ICUs)

It is very important for users' safety and comfort to be given, especially those who need mechanical ventilation. There have been more articles lately about dexmedetomidine, which may also help with agitation and delirium, though clinical trials have had mixed results [10]. A big part of ICU care is making sure that pain management works well. Up to 70% of patients may also feel moderate to severe pain after surgery while they are in the ICU, according to studies. Clearly, this shows how important it is to have enough sedatives and analgesics to effectively treat pain.

2.1. Importance of breastfeeding and its benefits

There is no better food for babies than breast milk. It gives them all the vitamins and strength infants need. Kids who are fed breast milk do better on IQ tests and are much less likely to be overweight or get diabetes as adults. Cancers of the breast and ovaries are also less likely to happen to women who breastfeed. Less than half of babies younger than 6 months around the world are exclusively breastfed, which is worse than what the WHO says should happen. A child is less likely to get common childhood illnesses from breast milk. The Maternity Practices in Infant Nutrition and Care (mPINC) survey can be used by hospitals to help mothers breastfeed [16].

2.2. Why do we have to know about effects of drugs on the breast milk composition?

Medications, especially analgesics and anaesthetics, getting into breast milk is a tricky issue that needs a lot of thought. There isn't a lot of biological information on the transfer of anaesthetic and analgesic pills into breast milk because it's hard to do research on breastfeeding women and their babies in a sensible and ethical way. “Pump and unload" after anaesthesia was given as if it were advice from beyond the grave before there were enough statistics on how drugs build up in breast milk. This isn't done very often anymore, and there may be proof that the highest doses of anaesthetic drugs are safe for breastfeeding and have low relative infant doses (RID) [15].

Most drugs used for anaesthesia are safe for breastfeeding, and most mothers can start breastfeeding again as soon as they recover from anaesthesia. The LactMed database and other tools give doctors up-to-date information on how drugs get into breast milk, which can help them make smart decisions. The result shows how important it is to keep studying and keeping our sources up to date in order to better understand how drugs, mostly analgesics and anaesthetics, can get into breast milk and affect breastfeeding and the infant's health [15]. It is very important to look into how analgesics and anaesthesia affect breast milk and breastfeeding for a number of reasons [17]. Babies are very sensitive to the effects of drugs because their bodies and organs are still developing. For the safety of infants, it is very important to know how the drugs enter their bodies and affect them.

Women who are breastfeeding may also need to be sedated or given anaesthesia, and they need facts-based information to make smart choices about breastfeeding after surgery [18]. Doctors and nurses often don't know what to say when they try to talk to breastfeeding moms about medications. Statistics on the amount of drug in breast milk and the relative infant dose (RID) help physicians figure out how dangerous the drug is for the baby [19].

This review helps in identifying anaesthesia and analgesia drugs that are transferred into breast milk and evaluating the impact of transferred medications on breast milk composition and assessing the potential effects of medication transfer on neonatal health and development.

Antibiotics are frequently given in intensive care units (ICUs). Some antibiotics may be observed in breast milk, however most of them had been observed to be secure for breastfeeding moms and their babies [25] . Antiviral tablets do not get into breast milk very often, but no person actually is aware of what the long-term consequences are on babies.

There is limited knowledge regarding the transfer of blood pressure medications into breast milk and their impact on infants. Therefore, further research is necessary to gain a better understanding. The impact of biological tablets on breast milk is currently uncertain, necessitating further research to determine their safety for infants who are breastfed. Insufficient data exists to fully understand the mechanisms by which GLP-1 agonists are transferred to breast milk and the potential impact they may have on infants [26]. While certain antifungal tablets are believed to be safe for use during breastfeeding, it is important to closely monitor the baby for any potential adverse effects, as is the case with any medication. Recent research has demonstrated that mRNA COVID-19 vaccines no longer transfer the vaccine particles into breast milk. Nevertheless, breast milk does transmit antibodies, which can be specifically beneficial for the infant receiving it [27]. With the advent new drugs in pharmaceutical era, new studies and guidelines are needed all the time to keep the best standards of care [29].

Table 2 Data of commonly used drugs in anaesthesia, ICU and HDU

Drug	Group	Transfer into Breast Milk	Potential Effects on Infants
Lidocaine	Local Anaesthetics	Yes	Generally considered safe
Bupivacaine	Local Anaesthetics	Yes	Generally considered safe
Ropivacaine	Local Anaesthetics	Yes	Generally considered safe
Procaine	Local Anaesthetics	Yes	Generally considered safe
Thiopental	Anaesthetics	Yes	Sedation, respiratory depression
Etomidate	Anaesthetics	Variable	Sedation, respiratory depression
Ketamine	Anaesthetics	Yes	Sedation, dissociation
Midazolam	Anaesthetics	Yes	Sedation, respiratory depression
Dexmedetomidine	Anaesthetics	Yes	Sedation, bradycardia
Meperidine	Opioids	Minimal	feeding difficulties
Pethidine	Opioids	passes into breast milk	Sedation, respiratory depression, feeding difficulties
Methadone	Opioids	Variable	Sedation, respiratory depression
Codeine	Opioids	Minimal	Respiratory depression, sedation
Fentanyl	Opioids	Yes	Moderate to high
Hydromorphone	Opioids	Yes	Moderate
Oxycodone	Opioids	Yes	Low
Midazolam	Benzodiazepines	Minimal Amount	Respiratory depression
Diazepam	Benzodiazepines	Detectable amounts	Sedation, poor feeding, respiratory depression
Cimetidine	Histamine Blockers	low amount	Gastrointestinal disturbances
Famotidine	Histamine Blockers	low amount	Drowsiness, gastrointestinal issues
Ranitidine	Histamine Blockers	low amount	Fussiness, gastrointestinal issues
Aspirin	NSAIDs	low amount	Reye's syndrome, bleeding disorders
Ibuprofen	NSAIDs	Minimal	Gastric irritation
Indomethacin	NSAIDs	Minimal	Gastric irritation, bleeding
Mefenamic acid	NSAIDs	Minimal	Gastric irritation
Naproxen	NSAIDs	Variable	Gastrointestinal irritation
Ketorolac	NSAIDs	Yes	Moderate
Diclofenac	NSAIDs	Yes	Low
Piroxicam	NSAIDs	Minimal	Gastrointestinal irritation, bleeding
Paracetamol	Analgesics	Yes	Generally considered safe
Sumatriptan	Triptans	Variable	Limited data available
Gentamicin	Antibiotics	Minimal	Low risk for infants
Cephalosporins	Antibiotics	Variable	Generally well-tolerated
Fluoroquinolones	Antibiotics	Variable	Generally low risk

Macrolides	Antibiotics	Variable	Generally well-tolerated
Penicillin	Antibiotics	low amount	Generally well-tolerated
Tetracyclines	Antibiotics	moderate amount	Potential risk for bone development
Piperacillin	Antibiotics	Yes	Low
Trimethoprim-sulfamethoxazole	Antibiotics	Yes	Moderate
Trimethoprim	Antibiotics	Yes, low amount	Generally well-tolerated
Metronidazole	Antibiotics	Yes	Low
Metronidazole	Antibiotics	Yes	Moderate
Rifabutin	Antibiotics	Yes	Low
Linezolid	Antibiotics	Yes	Low
Minocycline	Antibiotics	moderate amount	Risk of discoloration in infants
Acyclovir	Antivirals	Low	Generally considered safe
Oseltamivir	Antivirals	Yes	Low
Lamivudine	Antivirals	Yes	Low
Entecavir	Antivirals	Yes	Low
Tenofovir	Antivirals	Yes	Low
Warfarin	Anticoagulants	No	Not applicable
Carbamazepine	Antiepileptics	moderate amount	Generally well-tolerated
Lamotrigine	Antiepileptics	moderate amount	Generally well-tolerated
Phenobarbitone	Antiepileptics	high amount	Risk of sedation and respiratory depression
Phenytoin	Antiepileptics	moderate amount	Risk of developmental delay and cognitive impairment
Sodium valproate	Antiepileptics	high amount	Risk of developmental delay and cognitive impairment
Vigabatrin	Antiepileptics	low amount	Risk of vision problems in infants
Amitriptyline	Antidepressants	moderate amount	Potential sedation and irritability
Nortriptyline	Antidepressants	moderate amount	Potential sedation and irritability
Domperidone	Antiemetics	low amount	Generally well-tolerated
Metoclopramide	Antiemetics	moderate amount	Potential sedation and irritability
Loratadine	Antihistamines	No	Limited to no known effects on infants
Chlorpromazine	Antipsychotics	moderate amount	Potential sedation and irritability
Haloperidol	Antipsychotics	low amount	Potential central nervous system effects
Amiodarone	Antiarrhythmics	low amount	Limited data; monitor infant
Atenolol	Antihypertensives	low amount	Potential cardiovascular effects
Captopril	Antihypertensives	low amount	monitor infant
Digoxin	Cardiac medications	low amount	Potential cardiovascular effects
Diltiazem	Cardiac medications	low amount	Limited data; monitor infant

Enalapril	Cardiac medications	low amount	Limited data; monitor infant
Prednisone	Corticosteroids	Minimal	Limited data; monitor infant
Pseudoephedrine	Decongestants	Minimal	Potential stimulant effects
Isoflurane	Inhalation	Yes	Sedation, respiratory depression
Sevoflurane	Inhalation	Yes	Sedation, respiratory depression
Desflurane	Inhalation	Yes	Sedation, respiratory depression
Nitrous Oxide (N2O)	Inhalation	Minimal	Generally considered safe
Succinylcholine	Neuromuscular Blockers	Minimal	Generally considered safe
Rocuronium	Neuromuscular Blockers	Minimal	Generally considered safe
Vecuronium	Neuromuscular Blockers	Minimal	Generally considered safe
Atracurium	Neuromuscular Blockers	Minimal	Generally considered safe
Cisatracurium	Neuromuscular Blockers	Minimal	Generally considered safe
Duloxetine	Antidepressants	Yes	Low to moderate
Clonidine	Alpha Agonists	Yes	Low
Carbapenems	Carbapenems	Yes	Low
Aztreonam	Monobactams	Yes	Low
Vancomycin	Glycopeptides	Yes	Low
Teicoplanin	Glycopeptides	Yes	Low
Gentamicin	Aminoglycosides	Yes	Low
Ciprofloxacin	Fluoroquinolones	Yes	Low
Levofloxacin	Fluoroquinolones	Yes	Low
Amphotericin B	Antifungals	Yes	Low
Fluconazole	Antifungals	Yes	Moderate
Itraconazole	Antifungals	Yes	Low
Micafungin	Antifungals	Yes	Low
Chloroquine	Antiparasitic	Yes	Low
Atovaquone	Antiparasitic	Yes	Low
Albendazole	Antiparasitic	Yes	Low
Praziquantel	Antiparasitic	Yes	Very low
Ivermectin	Antiparasitic	Yes	Low
Isoniazid	Antituberculosis	Yes	Low
Rifampicin (Rifampin)	Antituberculosis	Yes	Low
Pyrazinamide	Antituberculosis	Yes	Low
Ethambutol	Antituberculosis	Yes	Low

Pfizer-BioNTech (Comirnaty)	Vaccines	Yes	Low
AstraZeneca	Vaccines	Yes	Low

3. Discussion

Based on our review of the literature, most drugs used for anaesthesia and pain are found in small amounts in breast milk, which are usually not thought to be clinically significant. This is in line with the guidelines that say breastfeeding can usually continue after anaesthesia without having to throw away the milk. But with some drugs, like opioids and benzodiazepines, you should be careful, especially after multiple doses and in babies up to 6 weeks old [29]. Several things affect how drugs get into breast milk. These include the drug's molecular weight, degree of ionisation, protein binding in blood and lipid solubility. The mother's metabolism and the baby's age and health are also very important factors. [30].

For clinical use, these results suggest that most drugs used during anaesthesia don't pose much of a risk to breastfeeding babies, but each case needs to be looked at separately. Anaesthesiologists should talk to lactating mothers who are going to have surgery about the relative infant dose (RID) of the drugs women are given. Using more than one method to treat pain after surgery can cut down on the need for opioids, which lowers the risk of respiratory depression in infants.

Future research has to attempt to fill the gaps in what is known, mainly about the long-term results of drug exposure via breast milk and making better hints for the way to take care of ICU parturient who are breastfeeding [30].

There should be guidelines in place in every hospital to help and explain our lactating mothers the strategies to minimize infant drug exposure. Each case should be evaluated individually, with a focus on minimizing infant drug exposure while managing maternal pain and recovery effectively. [26], [29].

4. Conclusion

This review article highlights the significance of understanding how medications affect breast milk and lactation for mothers in the ICU. The main findings suggest that issues such as difficulty expressing milk, medication transfer to breast milk, and emotional stress affect both the mother's and the infant's well-being. These challenges necessitate a treatment approach that focuses on techniques and medication management. The implications of these discoveries are profound. In the ICU, lactating mothers must strike a balance between taking medications and ensuring the safety and supply of breast milk. Healthcare professionals need to handle this complexity with care and accuracy making sure that both the mother and baby receive the best treatment. It is important for future studies to concentrate on creating guidelines for using medications while breastfeeding in care units taking into account the unique ways drugs work in women, after childbirth and their babies. Furthermore, exploring ways to design ICU and anaesthesia settings that cater to the needs of breastfeeding mothers could greatly enhance care. By addressing these areas of need we can enhance the support system for breastfeeding mothers in care ultimately improving the well-being and recovery of both mother and child.

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