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Hale's Medications & Mothers' Milk™

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Thomas W. Hale, RPh, PhD
Kaytlin Krutsch, PharmD, MBA, BCPS

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2023

A Manual of Lactational Pharmacology

Twentieth Edition

Thomas W. Hale, RPh, PhD
University Distinguished Professor
InfantRisk Center
Department of Pediatrics
Texas Tech University Health Sciences Center
School of Medicine
Amarillo, Texas

Kaytlin Krutsch, PharmD, MBA, BCPS
Assistant Professor
InfantRisk Center
Department of Obstetrics and Gynecology
Texas Tech University Health Sciences Center
School of Medicine
Amarillo, Texas

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Contents

Changes to This Edition

It seems the release of new drugs continues to increase each year, although the data published in breastfeeding mothers are still minimal. This new 2023 edition has many significant updates including the following.

New Drugs Added: 72

Drugs Updated With New Data: 356

Drugs With Updated LRC: 74

Drugs Updated Due to FDA Updates: 3

Drugs Updated With New Information: 927

Drug References Updated: 149

Each year there are so many new FDA-approved medications that it is difficult to choose which to add. As usual, we chose those that a breastfeeding mother would most likely use. Our laboratories have been publishing many new breastfeeding drug studies, and we have added all of these new studies. There has been an outpouring of new monoclonal antibodies approved recently. To keep up with these drugs, we've created a consolidated monograph and new table in the appendix to review those that have not been studied in breastfeeding.

We've added more than 72 new drugs, even though we don't know if and how much many transfer into human milk. We tried to evaluate the relative risk of each drug and provided a lactation risk category.

Each year more than 3 million mothers visit the InfantRisk website seeking information about drugs and pregnancy and breastfeeding. So many breastfeeding mothers have volunteered for our drug studies that we simply can't collect from all of them. But from these wonderful volunteers come the many new studies from our laboratories.

Thanks to all the lactation consultants and healthcare professionals that have helped us recruit patients for our studies. We will continue to pour out new studies that help moms continue breastfeeding their wonderful infants.

Thomas W. Hale & Kaytlin Krutsch

Preface

Introduction

It's now well known that human milk is the best nutrition for infants. The benefits are simply enormous and supported by a world of excellent literature. Further, it is becoming more and more apparent that breastfeeding has long-lasting health benefits for the mom. However, the use of medications in breastfeeding mothers is often controversial and is steeped with misinformation in the healthcare field. This book has for many years been the primary source for drug information and in breastfeeding mothers. The truth is, most drugs simply don't enter milk in levels that are hazardous to a breastfed infant. The problem, however, is determining which drugs are safe and which are hazardous.

Because so few clinicians understand lactational pharmacology, the number of women who are advised to discontinue breastfeeding in order to take a medication is still far too high. Fortunately, many mothers are now becoming aware of the enormous benefits of breastfeeding and simply refuse to follow some of the advice given by their healthcare professionals. They seek out the information on their own and invariably find this book or my websites.

Because almost all mothers will ingest medications during the early neonatal period, it is not surprising that one of the most common questions encountered in pediatrics concerns the use of various drugs in the breastfeeding mother. Unfortunately, most healthcare professionals simply review the package insert or advise the mother not to breastfeed without having done a thorough study of the literature to find the true answer. Discontinuing breastfeeding is often the wrong decision, and most mothers could easily continue to breastfeed and take the medication without risk to the infant. Even the FDA has recognized this and now recommends drug manufacturers carry out studies to determine milk levels of their drug.

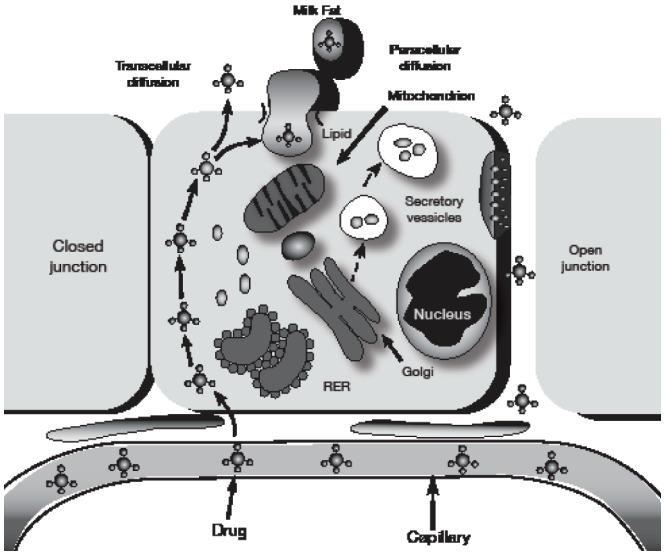
It is generally accepted that all medications transfer into human milk to some degree, although it is almost always quite low. Only rarely does the amount transferred into milk produce clinically relevant doses in the infant. Ultimately, it is the clinician's responsibility to review the research and make a clear decision as to whether the mother should continue to breastfeed.

Drugs may transfer into human milk if they:
Attain high concentrations in maternal plasma
Are low in molecular weight (<500 Da)
Are low in protein binding
Pass into the brain easily

However, once medications transfer into human milk, other kinetic factors are involved. One of the most important 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.

Drugs normally enter milk by passive diffusion, driven by equilibrium forces between the maternal plasma compartment and the maternal milk compartment. They pass from the maternal plasma through capillaries into the lactocytes lining the alveolus. Medications must generally pass through both bilayer lipid membranes of the alveolar cell to penetrate milk; although early on, they may pass between the alveolar cells (first 72 hours postpartum). During the first three days postpartum, large gaps between the alveolar cells exist. These gaps permit enhanced access into the milk for most drugs, many immunoglobulins, maternal living cells (lymphocytes, leukocytes, macrophages), and other

maternal proteins. By the end of the first week, the alveolar cells swell under the influence of prolactin and subsequently close the intracellular gaps thus reducing the transcellular entry of most maternal drugs, proteins, and other substances into the milk compartment. While it is generally agreed that medications penetrate into milk at higher levels during the colostral period, nevertheless, the absolute dose transferred during the colostrum period is still low due to the minimal volume of colostrum (30-100 mL/day) for the first few days postpartum.



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 the 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 a medication begins to fall, equilibrium forces drive the medication out of the milk compartment back into the maternal plasma for elimination. Maternal plasma levels are almost always directly related to the maternal drug dose. Higher doses produce higher plasma levels, and therefore higher milk levels. It is always recommended to use drug doses evaluated in lactation studies. We often see doses up to five times higher than those researched, limiting the generalizability of the findings.

In some instances, drugs may be trapped in milk (ion trapping) due to the lower pH of human milk (7.2). Drugs with a high pKa may become trapped in the milk compartment due to ion trapping. This is important in weakly basic drugs, such as the barbiturates (drugs with high pKa).

There are some known cellular pumping systems that actively pump drugs into milk. The most important is iodine. The iodine pump is the same as found in everyone's thyroid gland. Its purpose is to make sure the infant receives iodine to maintain thyroxine production.

The iodides, such as ^{131}I or any "ionic" form of iodine, concentrate in milk due to this pump. Thus iodides, particularly radioactive ones, should be avoided as their milk concentrations are exceedingly high. Two other physicochemical factors are important in evaluating drugs in breastfeeding mothers—the degree of protein binding and lipid solubility. Drugs that are very lipid soluble penetrate into milk in higher concentrations almost without exception. Of particular interest are the drugs that are active in the central nervous system (CNS). CNS-active drugs invariably have the unique characteristics required to enter milk. Therefore, if a drug is active in the central nervous system, significant levels in milk can be expected; although, the amounts still are often subclinical. Many of the neuroactive drugs produce Relative Infant Doses of >5%. Protein binding also plays an important role. Drugs circulate in the maternal plasma, either bound to albumin or freely soluble in the plasma. It is the free component (unbound fraction) that transfers into milk, while the bound fraction stays in the maternal circulation. Therefore, drugs that have high maternal protein binding (warfarin, most

NSAIDs) have low milk levels simply because they are bound in the plasma compartment and can't get out.

Once a drug has entered the mother's milk and has been ingested by the infant, it must traverse through the infant's GI tract prior to absorption. Some drugs are poorly stable in this environment due to the proteolytic enzymes and acids present in the infant's stomach. This includes the aminoglycoside family, omeprazole, and large peptide drugs, such as heparin, and most of the new monoclonal antibodies. Other drugs are poorly absorbed by the infant's gastrointestinal tract and do not enter the infant's blood stream. Thus, oral bioavailability is a useful tool to estimate just how much of the drug will be absorbed by the infant. Many drugs are sequestered in the liver (first pass) and may never actually reach the plasma compartment. Absorption characteristics such as these ultimately tend to reduce the overall effect of many drugs in breastfed infants. There are certainly exceptions to this rule, and one must always be aware that the action of a drug in the GI tract can be profound, producing diarrhea, constipation, and occasionally syndromes such as pseudomembranous colitis.

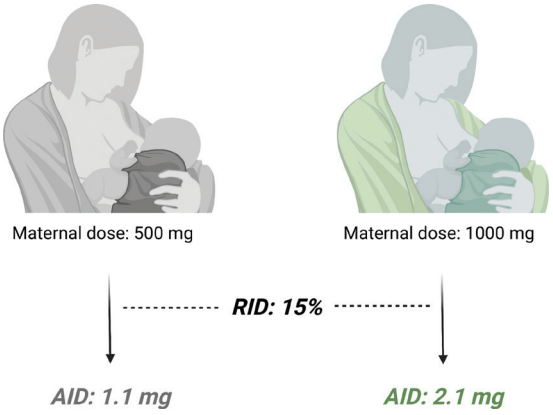
One of the more popular methods for estimating risk to the infant is the Relative Infant Dose (RID). The RID is calculated by dividing the infant's dose via milk (mg/kg/day) by the mother's dose in mg/kg/day. The RID gives the clinician a feeling for just how much medication the infant is exposed to on a weight-normalized basis. However, many authors calculate the infant dose without normalizing for maternal and infant weight, so be cautious. An RID has other limitations as well. It estimates infant exposure, but does not consider infant absorption. The RID also does not consider a comparative maternal dose. For example, a mother who doubles her dose still doubles the estimated exposure (Absolute Infant Dose or AID) to the infant as the RID stays the same.

Relative Infant Dose

$$RID = \frac{\text{Dose.infant } \frac{mg/kg}{d}}{\text{Dose.mother } \frac{mg/kg}{d}}$$

Dose.infant = dose in infant

Dose.mother = dose in mother



Key Points About Breastfeeding and Medications

- Avoid using medications that are not necessary. Herbal drugs, high-dose vitamins, unusual supplements, iodine supplements, zinc supplements, etc. that are simply not necessary should be avoided.
- If the Relative Infant Dose is less than 10%, most medications are considered relatively safe to use, but again this is dependent on the type of drug taken.
- Choose drugs for which we have published data, at studied doses, rather than those recently introduced.
- Evaluate the infant for risks. Be more cautious with premature infants or neonates.
- Medication used in the first three to four days generally produce subclinical levels in the infant due to the limited volume of milk.
- Recommend that mothers with symptoms of depression or other mental disorders seek treatment. Most of the medications used to treat these syndromes are safe. **Remember, healthy moms make healthy babies.**
- Most drugs are quite safe in breastfeeding mothers, while the hazards of using formula are well known and documented. Use donor human milk when the drug is potentially dangerous.
- With some medications, discontinuing breastfeeding for some hours/days may be required, particularly with radioactive compounds, and anticancer drugs. If the drug is hazardous to you, it is probably hazardous to your infant.
- Choose drugs with short half-lives, high protein binding, low oral bioavailability, or high molecular weight.

Lastly, it is very important to always evaluate the infant's ability to handle small amounts of medications. Some infants, such as premature or unstable infants, may not be suitable candidates for certain medications. But remember that early postpartum (and in late stage lactation), the amount of milk produced (30-100 mL/day) is so low that the clinical dose of drug transferred is often low, so even premature neonates would receive only a limited amount from the milk.

Evaluation of the Infant

- Inquire about the infant—always inquire as to the infant's age, size, and stability. This is perhaps the most important criterion to be evaluated prior to using the medication.
- Infant age—premature and newborn infants are at somewhat greater risk. Over half of reported adverse events happen within the first four weeks of age. Only 1 in 5 reports occur after the first 8 weeks. Older infant are at somewhat lower risk due to high metabolic capacity. Infants breastfeeding once or twice a day are at very low risk.
- Infant stability—unstable infants with poor GI stability may be at increased risk from certain medications.
- Pediatric Approved Drugs—generally are less hazardous if long-term history of safety is recognized.
- Dose vs Age—the age of an infant is critical. Use medications cautiously in premature infants. Older, mature infants can metabolize and clear medications much easier. Remember the dose of the drug the infant receives is dependent on the milk supply. In mothers in late stage lactation (>1 year), milk production is often low, so the dose of drug delivered is low as well.
- Drugs that alter milk production may profoundly affect infant growth and development—avoid medications that may alter the mother's milk production. These include estrogens, ergot alkaloids, and other drugs.

General Suggestions for the Clinician

Determine if the drug is absorbed from the GI tract. Many drugs, such as the aminoglycosides, vancomycin, cephalosporin antibiotics (third generation), magnesium salts, monoclonal antibodies, and large protein drugs (heparin), are so poorly absorbed that it is unlikely the infant will absorb significant quantities. At the same time, observe for GI side effects from the medication trapped in the GI compartment of the infant (e.g. diarrhea).

Review the Relative Infant Dose (RID) and compare that to the pediatric dose if known. Most older RIDs were derived using the C_{max} (highest milk concentration of the drug) that were published. In current research projects, we always calculate the average (C_{ave}) milk level throughout the dosing schedule. This estimate provided and average exposure rather than just the highest. we no longer use the milk/plasma ratio as it is virtually worthless unless you know the maternal plasma level. It does not provide the clinician with information as to the average amount of drug transferred to the infant via milk. Even if the drug has a high milk/plasma ratio, if the maternal plasma level of the medication is very small (such as with ranitidine), then the absolute amount (dose) of a drug delivered to the infant will still be quite small and often subclinical. Also consider the doses used in milk research versus the maternal dose being used in practice. Some drugs are used at significantly higher doses, and will result in a higher absolute amount of drug delivered to the infant.

Be cautious of drugs (or their active metabolites) that have long pediatric half-lives as they can continually build up in the infant's plasma over time. The barbiturates, benzodiazepines, and meperidine are classic examples where higher levels in the infant can and do occasionally occur. Interestingly, the SSRI family have long half-lives, but are not retained in the infant's plasma.

If you are provided a choice, choose drugs that have higher protein binding because they are generally sequestered in the maternal circulation and do not transfer readily into the milk compartment or the infant. Remember, it's the free drug that transfers into the milk compartment. Without doubt, the most important parameter that determines drug penetration into milk is plasma protein binding. Choose drugs with high protein binding.

Although not always true, we have generally found centrally active drugs (anticonvulsants, antidepressants, antipsychotic) frequently penetrate milk in higher (not necessarily "high") levels simply due to their physicochemistry. If the drug in question produces sedation, depression, or other neuroleptic effects in the mother, it may produce similar effects in the infant. Thus, with CNS-active drugs, one should always check the data in this book closely and monitor the infant routinely.

For radioactive compounds, we have gathered much of the published data in this field into several tables. The Nuclear Regulatory Commission recommendations are quite good, but they differ from some published data. They can be copied and provided to your radiologist. They are available from the Nuclear Regulatory Commission's web page address in the appendix. With radioisotopes, we recommend you routinely call the InfantRisk Center for advice. Some are quite dangerous.

Use the Relative Infant Dose. In general, a Relative Infant Dose of <10% is considered safe, and its use is becoming increasingly popular by numerous investigators. But this depends on the drug. With risky anticancer drugs, a much lower RID is should be used in your evaluation of risk.

Most importantly, it is rare that a breastfeeding mother needs to discontinue breastfeeding just to take a medication. It is simply not acceptable for the clinician to stop lactation merely because of heightened anxiety or ignorance on their part. The risks of formula feeding are significant and should not be trivialized. Few drugs have documented side effects in breastfed infants, and we know most of these.

The following review of drugs is a thorough review of what has been published and what we presently know about the use of medications in breastfeeding mothers.

The authors make no recommendations as to the safety of these medications during lactation in clinical practice, but only review what is currently published in the scientific literature. Individual use of medications must be left up to the judgement of the physician, the patient, and other healthcare consultants.

Thomas W. Hale & Kaytlin Krutsch

How to Use This Book

This section of the book is designed to aid the reader in determining risk to an infant from maternal medications and in using the pharmacokinetic parameters throughout this reference.

Drug Name and Generic Name:

Each monograph begins with the generic name of the drug. The most common trade names are provided under the Trade section. With some pharmaceuticals, there may be more than one drug added to the product. In this case we have added a table called "Combination Drugs" in the appendix where all the drugs present in that specific pharmaceutical are listed and you can then look up the individual products.

Other Trades:

This book is used all over the world. Thus many other trade names from other countries are now included in this section.

Category:

This lists the class or "family of drugs" that the medication belongs to and gives a general idea of the pharmacology, mechanism of action, and probable use of the drug.

Drug Monograph:

The drug monograph lists what we currently understand about the drug, its ability to enter milk, the concentration in milk at set time intervals, and other parameters that are important to a clinical consultant. We have attempted at great length to report only what the references have documented.

Dr. Hale's Lactation Risk Categories:

L1 Compatible:

Drug which has been taken by a large number of breastfeeding mothers without any observed increase in adverse effects in the infant. Controlled studies in breastfeeding women fail to demonstrate a risk to the infant and the possibility of harm to the breastfeeding infant is remote; or the product is not orally bioavailable in an infant.

L2 Probably Compatible:

Drug which has been studied in a limited number of breastfeeding women without an increase in adverse effects in the infant. And/or, the evidence of a demonstrated risk which is likely to follow use of this medication in a breastfeeding woman is remote.

L3 Probably Compatible:

There are no controlled studies in breastfeeding women; however, the risk of untoward effects to a breastfed infant is possible, or controlled studies show only minimal non threatening adverse effects. Drugs should be given only if the potential benefit justifies the potential risk to the infant. (New medications that have absolutely no published data are automatically categorized in this category, regardless of how safe they may be.)

L4 Potentially Hazardous:

There is positive evidence of risk to a breastfed infant or to breast-milk production, but the benefits from use in breastfeeding mothers may be acceptable despite the risk to the infant (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective.)

L5 Hazardous:

Studies in breastfeeding mothers have demonstrated that there is significant and documented risk to the infant based on human experience, or it is a medication that has a high risk of causing significant damage to an infant. The risk of using the drug in breastfeeding women clearly outweighs any possible benefit from breastfeeding. The drug is contraindicated in women who are breastfeeding an infant.

Adult Concerns:

This section lists the most prevalent undesired or bothersome side effects listed for adults. As with most medications, the occurrence of these is often quite rare, generally less than 1%-10%. Side effects vary from one patient to another, with most patients not experiencing untoward effects.

Pediatric Concerns:

This section lists the side effects noted in the published literature as associated with medications transferred via human milk. Pediatric concerns are those effects that were noted by investigators as being associated with drug transfer via milk. In some sections, we have added comments that may not have been reported in the literature, but are well known attributes of this medication.

Infant Monitoring:

This section provides advice to the clinician regarding potential side effects that may occur in the infant from exposure to a medication in breast milk. The infant monitoring parameters can be used by the clinician to educate the mother about potential side effects that could occur in the infant.

Relative Infant Dose:

The Relative Infant Dose (RID) is calculated by dividing the infant's dose via milk in "mg/kg/day" by the maternal dose in "mg/kg/day" (see page 9). This weight-normalizing method indicates approximately how much of the "maternal dose" the infant is receiving. Many authors now use this calculation because it gives a better indication of the relative dose transferred to the infant. We report RID ranges, as this gives the reader an estimate of all the Relative Infant Doses published by the various authors.

Please understand, however, that many authors use different methods for calculating RID. Some are not weight-normalized. In these cases, their estimates may differ slightly from this book. While we often place the authors' estimates of Relative Infant Dose in the text, the RID range that we calculate is weight-normalized in all instances when the maternal weight is provided. So RID may be slightly different according to how it is calculated.

Many researchers now suggest that anything less than 10% of the maternal dose is probably safe. This is usually correct. However, some drugs (metronidazole, acetaminophen) actually have much higher Relative Infant Doses, but because they are quite non-toxic, they do not often bother an infant. To calculate this dose, we chose the data we felt was best, and this often included larger studies with AUC calculations of mean concentrations in milk. When maternal weights are not published, we choose an average body weight of 70 kg for an adult. Thus, most of the RIDs herein are calculated assuming a maternal average weight of 70 kg and a daily milk intake of 150 mL/kg/day in the infant.

Adult Dosage:

This is the usual adult oral dose provided in the package insert. While these are highly variable, wechose the dose for the most common use of the medication.

Alternatives:

Drugs listed in this section may be suitable alternate choices for the medication listed above. In many instances, if the patient cannot take the medication or it is a poor choice due to high milk concentrations, these alternates may be suitable candidates. WARNING: The alternatives listed are only suggestions and may not be at all appropriate for the syndrome in question. Only the clinician can make this judgment. For instance, nifedipine is a calcium channel blocker with good antihypertensive qualities, but poor antiarrhythmic qualities. In this case, verapamil would be a better choice.

T½=

This lists the most commonly recorded adult half-life of the medication. It is very important to remember that short half-life drugs are preferred. Use this parameter to determine if the mother can successfully breastfeed around the medication by nursing the infant, then taking the medication. If the half-life is short enough (1-3 hours), then the drug level in the maternal plasma will be declining when the infant feeds again. This is ideal. If the half-life is significantly long (12-24 hours) and if your physician is open to suggestions, then find a similar medication with a shorter half-life (compare ibuprofen with naproxen). However, in todays world, longer-half life drugs are preferred and we simply have to accomodate these and rely on published data.

Vd=

The volume of distribution is a useful kinetic term that describes how widely the medication is distributed in the body. Drugs with high volumes of distribution (Vd) are distributed in higher concentrations in remote compartments of the body and may not stay in the blood. Marijuana is a classic example.

Another such drug, digoxin enters the blood compartment and then rapidly leaves to enter the heart and skeletal muscles. Most of the drug is sequestered in these remote compartments (100-fold). Therefore, drugs with high volumes of distribution (1-20 L/kg) generally require much longer to clear from the body than drugs with smaller volumes (<1 L/kg). For instance, whereas it may only require a few hours to totally clear gentamycin (Vd = 0.28 L/kg), it may require weeks to clear amitriptyline (Vd = 10 L/kg). Further, some drugs may have one half-life for the plasma compartment, but may have a totally different half-life for the peripheral compartment, as half-life is a function of volume of distribution. We have found that drugs with high Vd generally produce lower milk levels. For a complete description of Vd, please consult a good pharmacology reference. In this text, the units of measure for Vd are L/kg.

T_{max}=

This lists the time interval from administration of the drug until it reaches the highest level in the mother's plasma (C_{max}), which we call the peak or "time to max", hence T_{max}. Occasionally, you may be able to avoid nursing the baby when the medication is at the peak. Rather, wait until the peak is subsiding or has at least dropped significantly. Remember, drugs enter breast milk as a function of the maternal plasma concentration. In general, the higher the mother's plasma level, the greater the entry of the drug into her milk. If possible, choose drugs that have short peak intervals, and suggest mom not breastfeed when the drug is at C_{max}.

MW=

The molecular weight of a medication is a significant determinant as to the entry of that medication into human milk. Medications with small molecular weights (<200 Da) can easily pass into milk by traversing small pores in the cell walls of the mammary epithelium (see ethanol). Drugs with higher molecular weights must traverse the membrane by dissolving in the cells' lipid membranes, which may significantly reduce milk levels. As such, the smaller the molecular weight, the higher the relative transfer of that drug into milk. Protein medications (e.g., heparin), which have enormous molecular weights, transfer at much lower concentrations and are virtually excluded from human breast milk. Therefore, when possible, choose drugs with higher molecular weights to reduce their entry into milk. A new class of drugs has risen in popularity in the last decade. These are the monoclonal antibodies. These very selective antibodies mostly derived from human IgG1-4, are used to treat a number of severe diseases, such as Crohn's disease, multiple sclerosis, rheumatoid conditions, migraine headache, etc. Interesly, IgG molecules are enormous in molecular weight (around 160,000 Da) and thus enter the milk compartment poorly. Further, they are largely destroyed by proteases in the GI tract of the infant if presented in milk. At this point, we do not think much, if any, of these monoclonals enter milk, or survive the GI tract of the infant. Thus far, all studies of these antibodies in human milk thus far, suggest levels in milk are far less than 1.0%, and virtually none of this would survive the GI tract of the infant. However, the use of these drugs in pregnant women in the last trimester, may produce significant plasma levels in the fetus, and thus the newborn infant. Thus some infants could be susceptible to problems associated with the fetal exposure to these drugs (immunosuppressed). Current data thus far does not suggest significant transfer of these products into human milk.

M/P=

This lists the milk/plasma ratio. This is the ratio of the concentration of drug in the mother's milk divided by the concentration in the mother's plasma. If high (>1-5), it is useful as an indicator of drugs that may sequester in milk in high levels. If low (<1), it is a good indicator that only minimal levels of the drug are transferred into milk (this is preferred). While it is best to try to choose drugs with LOW milk/plasma ratios, the amount of drug which transfers into human milk is largely determined by the level of drug in the mother's plasma compartment. Even with high M/P ratios and LOW maternal plasma levels, the amount of drug that transfers is still low. Therefore, the higher M/P ratios often provide an erroneous impression that large amounts of drug are going to transfer into milk. This simply may not be true.

PB=

This lists the percentage of maternal protein binding. Most drugs circulate in the blood bound to plasma albumin and other proteins. If a drug is highly protein bound, it cannot enter the milk compartment as easily. The higher the percentage of binding, the less likely the drug is to enter the maternal milk. Try to choose drugs that have high protein binding in order to reduce the infant's exposure to the medication. Good protein binding is typically greater than 90%.

Oral=

Oral bioavailability refers to the ability of a drug to reach the systemic circulation after oral administration. It is generally a good indication of the amount of medication that is absorbed into the blood stream of the patient. Drugs with low oral bioavailability are generally either poorly absorbed in the gastrointestinal tract, are destroyed in the gut, or are sequestered by the liver prior to entering the plasma compartment. The oral bioavailability listed in this text is the adult value; almost none have been published for children or neonates. Recognizing this, these values are still useful in estimating if a mother or perhaps an infant will actually absorb enough drug to provide clinically significant levels in the plasma compartment of the individual. The value listed estimates the percent of an oral dose that would be found in the plasma compartment of the individual after oral administration. In many cases, the oral bioavailability of some medications is not listed by manufacturers, but instead terms

such as “Complete,” “Nil,” or “Poor” are used. For lack of better data, we have included these terms when no data are available on the exact amount (percentage) absorbed.

pKa=

The pKa of a drug is the pH at which the drug is equally ionic and nonionic. The more ionic a drug is, the less capable it is of transferring from the milk compartment to the maternal plasma compartment. Hence, the drug becomes trapped in milk (ion-trapping). This term is useful because drugs that have a pKa higher than 7.2 may be sequestered to a slightly higher degree than one with a lower pKa. Drugs with higher pKa generally have higher milk/plasma ratios. Hence, choose drugs with a lower pKa.

With many drugs, the pharmacokinetics have not been described or published. In this case we leave this entry blank.

Common Abbreviations

ACEI	Angiotensin converting enzyme inhibitor
AUC	Area under the curve
BID	Twice daily
Cmax	Plasma or milk concentration at peak
d	Day
Da	Dalton
et al.	"and others"
g	Gram
GI	Gastrointestinal
h	Hour
LRC	Lactation risk category
M/P	Milk/plasma ratio
MAOI	Monoamine oxidase inhibitors
mg/L	Milligram per liter
mL	Milliliter (1 cc)
mmol	Millimole of weight
MW	Molecular weight
ng/L	Nanogram per liter
NR	Not rated
NSAIDs	Nonsteroidal anti-inflammatory drug
Oral	Oral bioavailability (adult)
PB	Percent of protein binding in maternal circulation
pg	Picogram
PHL	Pediatric elimination half-life
PRN	As needed
QD	Daily
QID	Four times daily
RID	Relative infant dose
SNRIs	Serotonin norepinephrine reuptake inhibitors
SSRIs	Selective serotonin reuptake inhibitors
T½	Adult elimination half-life
TCAs	Tricyclic antidepressants
TID	Three times daily
Tmax	Time to peak plasma level (PK)
Vd	Volume of distribution
X	Times
mCi	Millicurie of radioactivity
µCi	Microcurie of radioactivity
µg/L	Microgram per liter
µmol	Micromole of weight

Hale's

Medications & Mothers' Milk

2023

A Manual of Lactational Pharmacology

ABACAVIR

Trade: Ziagen

Category: Antiviral

LRC: L5 - Limited Data-Hazardous if Maternal HIV Infection

Abacavir (ABC) is a nucleoside reverse transcriptase inhibitor (NRTI) that is used in combination with other agents for the treatment of HIV.[1]

In a study published in 2013, nine women receiving Trizivir (abacavir 300 mg + zidovudine 300 mg + lamivudine 150 mg) twice daily provided breast-milk samples for analysis on day 30 postpartum.[2] The median abacavir level was 0.057 µg/mL and the highest level was about 0.5 µg/mL. The milk/plasma ratio was found to be 0.85. A typical infant would receive 0.0086 mg/kg/day when using the median milk sample and about 0.075 mg/kg/day when using the highest concentration. This corresponds to a relative infant dose of 0.1% and 0.9%, respectively. Of the nine infants in the study who were exposed to abacavir, only one had a detectable concentration of abacavir in plasma. No side effects were reported in these infants. However, the authors of this study raised the possibility of subinhibitory levels of abacavir promoting viral resistance to the drug, which could then affect the baby.

Note: This medication is an L5 to highlight the contraindication of breastfeeding when the mother is known to be infected with HIV; this medication is not an L5 based on its risk to the infant in breast milk. The Centers for Disease Control and Prevention recommend that HIV infected mothers do not breastfeed their infants to avoid postnatal transmission of HIV.

T 1/2	1.54 h	MW	670.74 Da	PB	50%
Tmax	0.7-1.7 h	RID	0.1%-0.88%	Vd	0.86 L/kg
Oral	83%	M/P		pKa	5.01

Adult Concerns: Headache, fatigue, depression, changes in sleep, abnormal dreams, nausea, vomiting, diarrhea, changes in liver function, elevated triglycerides, thrombocytopenia, severe rash.

Adult Dose: 300 mg twice a day or 600 mg daily.

Pediatric Concerns: In pediatric HIV clinical studies the most common side effects that occurred when this medication was administered directly to the infant (not via milk) included: fever and/or chills, nausea, vomiting, diarrhea, skin rashes, and ear/nose/throat infections.

Infant Monitoring: Breastfeeding is not recommended in mothers who have HIV.

Alternatives:

References:

1. Pharmaceutical manufacturers prescribing information.
2. Shapiro RL, Rossi S, Ogwu A, et al. Therapeutic levels of lopinavir in late pregnancy and abacavir passage into breast milk in the Mma Bana Study, Botswana. Antivir Ther. 2013;18(4):585-590.

ABATACEPT

Trade: Orencia

Category: Antirheumatic

LRC: L3 - No Data-Probably Compatible

Abatacept is a soluble fusion protein that is linked to a modified portion of human immunoglobulin G1 (IgG1).[1] The apparent molecular weight of abatacept is 92,000 Daltons. Abatacept inhibits T cell activation by binding to CD80 and CD86 receptors which down regulates the T cells implicated in inflammation of rheumatic disorders. In vitro, abatacept decreases T cell proliferation and inhibits the production of the cytokines TNF alpha, interferon-gamma, and interleukin-2. There are no data on the transfer of this antibody into human milk. Due to its large molecular weight and poor oral absorption, it is not likely to enter breast milk or the infant's systemic circulation in clinically relevant amounts; however, there are no data to confirm this at this time.

T 1/2	13.1 days	MW	92,000 Da	PB	
Tmax		RID		Vd	0.02-0.13 L/kg
Oral	Nil	M/P		pKa	

Adult Concerns: Headache, fever, dizziness, cough, nausea, abdominal pain, back pain or limb pain, rash, antibody formation, increased risk of infection.

Adult Dose: 500-1000 mg IV at 0, 2, and 4 weeks, then repeat every 4 weeks.

Pediatric Concerns: No adverse effects have been reported via milk at this time.

Infant Monitoring:

Alternatives: Infliximab(L3), Etanercept(L2).

References:

1. Pharmaceutical manufacturers prescribing information.

ACARBOSE

Trade: Glucobay, Prandase, Precose

Category: Antidiabetic, other

LRC: L3 - No Data-Probably Compatible

Acarbose is an oral alpha-glucosidase inhibitor used to delay the absorption of carbohydrates in the management of Type II diabetes.[1,2] The local action of this medication in the gastrointestinal tract reduces carbohydrate absorption and the rapid rise in glucose and insulin following a meal; hence, glycosylated hemoglobin (HbA1c) levels are reduced over time. No data are available on the transfer of acarbose into human milk. The oral bioavailability of this medication is less than 2%, thus little medication would be expected to enter maternal milk.

T 1/2	~2 h	MW	645 Da	PB	
Tmax	~1 h	RID		Vd	0.32 L/kg
Oral	0.7%-2%	M/P		pKa	11.23

Adult Concerns: Abdominal pain, flatulence, diarrhea, increases in liver enzymes.

Adult Dose: 50-100 mg TID.

Pediatric Concerns: None reported via milk.

Infant Monitoring: Flatulence, persistent diarrhea, weight gain.

Alternatives: Insulin(L1), Metformin(L1), Glyburide(L2).

References:

1. Pharmaceutical manufacturers prescribing information.
2. Balfour JA, McTavish D. Acarbose. An update of its pharmacology and therapeutic use in diabetes mellitus. Drugs. 1993;46(6):1025-1054.

ACEBUTOLOL

Trade: Monitan, Sectral

Category: Beta Adrenergic Blocker

LRC: L3 - Limited Data-Probably Compatible

Acebutolol predominately inhibits beta-1 receptors, but can block beta-2 receptors at high doses.[1] It is low in lipid solubility, and contains intrinsic sympathetic activity (partial beta agonist activity). Studies indicate that on a weight basis, acebutolol is approximately 10%-30% as effective as propranolol.

In a study of seven women receiving 200-1200 mg/day acebutolol, the highest milk concentration occurred in the women receiving 1200 mg/day and was 4123 µg/L.[2] In women receiving 200, 400, or 600 mg/day of acebutolol, milk levels were 286 µg/L, 666 µg/L, and 539 µg/L, respectively. Adverse effects of beta-blockade were reported.

Acebutolol and its major active metabolite, diacetolol, appear in breast milk with a milk/plasma ratio of 1.9 to 9.2 (acebutolol) and 2.3 to 24.7 (diacetolol). These levels are considered relatively high and occurred following maternal doses of 400-1200 mg/day. When the metabolite is added, the infant dose may approach 10% of the maternal dose.

T 1/2	3-4 h	MW	336 Da	PB	26%
Tmax	2-4 h	RID	0.94%-3.61%	Vd	1.2 L/kg
Oral	35%-50%	M/P	7.1-12.2	pKa	13.91

Adult Concerns: Headache, dizziness, insomnia, depression, fatigue, chest pain, bradycardia, hypotension, heart failure, wheezing, vomiting, constipation, diarrhea, myalgia.

Adult Dose: 200-400 mg BID.

Pediatric Concerns: Hypotension, bradycardia, hypoxemia, and transient tachypnea have been reported.[2]

Infant Monitoring: Drowsiness, lethargy, pallor, poor feeding, and weight gain.

Alternatives: Labetalol(L2), Metoprolol(L2).

References:

1. Pharmaceutical manufacturers prescribing information.
2. Boutroy MJ, Bianchetti G, Dubruc C, Vert P, Morselli PL. To nurse when receiving acebutolol: is it dangerous for the neonate? Eur J Clin Pharmacol. 1986;30(6):737-739.

ACETAMINOPHEN (PARACETAMOL)

Trade: 222 AF Extra Strength, Abenol, Feverall, Actamin Maximum Strength, Panadol, Aminofen, Tylenol, Genapap

Category: Analgesic

LRC: L1 - Extensive Data-Compatible

Acetaminophen is an analgesic/antipyretic used in the treatment of fever and pain. When taken orally, only minimal amounts are secreted into breast milk and are considered too small to be hazardous. In a study of 11 mothers who received 650 mg of acetaminophen orally, the highest milk levels reported were from 10-15 mg/L.[1] The milk/plasma ratio was 1.08. In another study of three patients who received a single 500 mg oral dose, the reported milk and plasma concentrations of acetaminophen were 4.2 mg/L and 5.6 mg/L respectively.[2] The milk/plasma ratio was 0.76. The maximum observed concentration in milk was 4.4 mg/L. In another study of women who ingested 1000 mg acetaminophen, milk levels averaged 6.1 mg/L and provided an average dose of 0.92 mg/kg/day according to the authors.[3] Although there seems to be wide variation in the milk concentrations in these studies, the amount of acetaminophen an infant could ingest via breast milk is most likely significantly less than the pediatric therapeutic dose.

Acetaminophen is increasingly being used intravenously for the relief of moderate to severe pain conditions. Some reports have suggested that the analgesic efficacy of intravenous acetaminophen is equivalent to that of intravenous morphine, and is probably preferred due to its minimal side effects.[4,5] Following a 1 g IV dose of acetaminophen, the peak plasma concentrations attained are in the order of 28 mg/L at the end of 15 minutes. According to one report, following a 2 g IV dose of acetaminophen in postpartum mothers, the plasma levels decreased from 22.5 mg/L to 3.9 mg/L within 6 hours postdose.[6] Following a single IV dose, a maternal peak plasma concentration of 28 mg/L suggests that a breastfed infant would receive a dose of 19.6-28 mg/day (M/P ratio = 1) or about 4-6 mg/kg/day. This is far lower than the clinical doses for infants (10-15 mg/kg/dose).

The dose ingested could be higher in premature or younger infants, but would probably still be lower than the clinically used pediatric doses. Nevertheless, some caution is advised. IV acetaminophen has been successfully used in premature infants born at 25-32 weeks of gestation, without any reported side effects.[7] The serum concentrations at the end of 8-12 doses ranged between 8-64 mg/L. The authors reported that the infants tolerated the drug well. Based on these studies it may be said that infants seem to tolerate IV acetaminophen well. The dose ingested by an infant following IV acetaminophen in a lactating mother would most probably not be clinically relevant.

There is growing evidence that acetaminophen use may be linked to an increased prevalence of asthma among children and adults. In one published paper, it has been recommended that any child with asthma or a family history of asthma avoid using acetaminophen.[8] Prenatal exposure and exposure to acetaminophen in the first year of life has also been linked to development of asthma later in life.[9-13] Subsequently, the issue of lactational exposure to acetaminophen and its association with development of asthma has also been addressed.

In one such short-term study, out of 11 wheezing, exclusively breastfed infants, mothers of seven of the infants had admitted intake of acetaminophen at the time of onset of wheezing symptoms in the infants.[14] However, these claims have been refuted by a few other authorities, based on various grounds. Nevertheless, due to the immaturity of metabolic pathways in the infant, a customary recommendation of judicious use of medications (including acetaminophen), during lactation has been advocated.

T 1/2	2 h	MW	151 Da	PB	10%-25%
Tmax	10-60 min.	RID	6.41%-8.82%	Vd	0.8-1 L/kg
Oral	>85%	M/P	0.91-1.42	pKa	9.5

Adult Concerns: Few when taken in normal doses. Diarrhea, gastric upset. Note: numerous cases of liver toxicity have been reported following "chronic" use of acetaminophen at >200 mg/kg/day. Do not exceed 3000 mg in a 24-hour period or 1000 mg/dose. Exceedingly high doses can cause severe hepatic toxicity and death.

Adult Dose: 650 mg every 4-6 hours PRN.

Pediatric Concerns: None reported via milk at this time.

Infant Monitoring: Diarrhea, gastric upset; potential for liver toxicity if maternal overdose.

Alternatives: Ibuprofen(L1).

References:

1. Berlin CM Jr, Yaffe SJ, Ragni M. Disposition of acetaminophen in milk, saliva, and plasma of lactating women. Pediatr Pharmacol. 1980;1(2):135-141.
2. Bitzen PO, Gustafsson B, Jostell KG, Melander A, Wahlin-Boll E. Excretion of paracetamol in human breast milk. Eur J Clin Pharmacol. 1981;20(2):123-125.
3. Notarianni LJ, Oldham HG, Bennett PN. Passage of paracetamol into breast milk and its subsequent metabolism by the neonate. Br J Clin Pharmacol. July 1987;24(1):63-67.
4. Serinken M, Eken C, Turkcuer I, Elicabuk H, Uyanik E, Schultz CH. Intravenous paracetamol versus morphine for renal colic in the emergency department: a randomised double-blind controlled trial. Emerg Med J: EMJ. November 2012;29(11):902-905.
5. Craig M, Jeavons R, Probert J, Benger J. Randomised comparison of intravenous paracetamol and intravenous morphine for acute traumatic limb pain in the emergency department. Emerg Med J: EMJ. January 2012;29(1):37-39.
6. Kulo A, van de Velde M, de Hoon J, et al. Pharmacokinetics of a loading dose of intravenous paracetamol post caesarean delivery. Int J Obstet Anesth. April 2012;21(2):125-128.
7. van Ganzewinkel CJ, Mohns T, van Lingen RA, Derijks LJ, Andriessen P. Paracetamol serum concentrations in preterm infants treated with paracetamol intravenously: a case series. J Med Case Rep. 2012;6:1.
8. McBride JT. The association of acetaminophen and asthma prevalence and severity. Pediatrics. December 2011;128(6):1181-1185.
9. Eyers S, Weatherall M, Jefferies S, Beasley R. Paracetamol in pregnancy and the risk of wheezing in offspring: a systematic review and meta-analysis. Clin Exp Allergy: J Br Soc Allergy Clin Immunol. April 2011;41(4):482-489.
10. Edenoskdkan M, Sadatsafavi M, Jafari S, Doyle-Waters M, Aminzadeh K, Fitzgerald JM. Acetaminophen use and the risk of asthma in children and adults: a systematic review and metaanalysis. Chest. November 2009;136(5):1316-1323.
11. Rebordosa C, Kogevinas M, Sorensen HT, Olsen J. Pre-natal exposure to paracetamol and risk of wheezing and asthma in children: a birth cohort study. Int J Epidemiol. June 2008;37(3):583-590.
12. Shaheen SO, Newson RB, Henderson AJ, et al. Prenatal paracetamol exposure and risk of asthma and elevated immunoglobulin E in childhood. Clin Exp Allergy: J Br Soc Allergy Clin Immunol. January 2005;35(1):18-25.
13. Shaheen SO, Newson RB, Sherriff A, et al. Paracetamol use in pregnancy and wheezing in early childhood. Thorax. November 2002;57(11):958-963.
14. Verd S, Nadal-Amat J. Paracetamol and asthma and lactation. Acta paediatr. July 2011;100(7):e2-e3; author reply e3.

ACETAZOLAMIDE

Trade: Acetazolam, Dazamide, Diamox, Sequels

Category: Diuretic

LRC: L2 - Limited Data-Probably Compatible

Acetazolamide is a carbonic anhydrase inhibitor dissimilar to other thiazide diuretics. There are documented suggestions that diuretics in general decrease the volume of breast milk. In a patient who received 500 mg of acetazolamide twice daily, acetazolamide concentrations in milk were 1.3 to 2.1 mg/L while the maternal plasma levels ranged from 5.2-6.4 mg/L.[1] Plasma concentrations in the exposed infant were 0.2 to 0.6 µg/mL 2 to 12 hours after breastfeeding. These amounts are unlikely to cause adverse effects in the infant.

T 1/2	2.4-5.8 h	MW	222 Da	PB	70%-95%
Tmax	1-3 h	RID	1.37%-2.2%	Vd	0.2 L/kg
Oral	Complete	M/P	0.25	pKa	7.2

Adult Concerns: Anorexia, diarrhea, metallic taste, polyuria, muscular weakness, potassium loss. Malaise, fatigue, depression, renal failure have been reported.

Adult Dose: 500 mg BID.

Pediatric Concerns: None reported via milk.

Infant Monitoring: Observe for fluid loss, dehydration, lethargy.

Alternatives:

References:

1. Soderman P, Hartvig P, Fagerlund C. Acetazolamide excretion into human breast milk. Br J Clin Pharmacol. 1984;17(5):599-600.

ACETYLSALICYLIC ACID

Trade: Aspirin, ASA, Aspirtab, Ascriptin, Easprin, Ecotrin, Ecpirin, Entercote

Category: Analgesic

LRC: L2 - Limited Data-Probably Compatible

Acetylsalicylic acid (ASA) is an irreversible inhibitor of cyclooxygenase-1 and 2 (COX-1 and COX-2).[1] At low doses, COX-1 inhibition indirectly leads to decreased platelet aggregation. Anti-inflammatory, analgesic, and antipyretic

effects also emerge at higher doses. ASA is rapidly metabolized to salicylic acid, which is a lower-potency, reversible inhibitor of a variety of processes. Few harmful effects have been reported with use in lactation.

In one study, salicylic acid (active metabolite) penetrated poorly into milk (454 mg dose ASA), with peak levels of only 1.12 to 1.60 µg/mL, whereas maternal peak plasma levels were 33 to 43.4 µg/mL.[2] In another study of a rheumatoid arthritis patient who received 4 g/day ASA, none was detectable in her milk (<5 mg/100 mL).[3] Extremely high doses in the mother could potentially produce slight bleeding in the infant. Because ASA is implicated in Reye syndrome, it is a poor choice of analgesic to use in breastfeeding mothers. However, in rheumatic fever patients, it is still one of the anti-inflammatory drugs of choice and a risk-versus-benefit assessment must be done in this case.

In a study of a patient consuming ASA chronically, salicylate concentrations in milk peaked at 3 hours at a concentration of 10 mg/L following a maternal dose of 975 mg.[4] Maternal plasma levels peaked at 2.25 hours at 108 mg/L. The milk/plasma ratio was reported to be 0.08. In a study of eight women following the use of 1 g (about three 325 mg tablets) oral doses of ASA, average milk levels of salicylic acid (active metabolite) were 2.4 mg/L at 3 hours.[5] The metabolite salicyluric acid, reached a peak of 10.2 mg/L at 9 hours. Averaging total salicylates and salicyluric acid metabolites, the author suggests the relative infant dose would be 9.4% of the maternal dose.

In a new study in seven breastfeeding mothers consuming 81 mg/day, milk samples were collected at 0, 1, 2, 4, 8, 12, and 24 hours.[6] Acetylsalicylic acid levels were below the limit of quantification (0.61 ng/mL) in all the milk samples, whereas salicylic acid was detected at very low concentrations. The average concentration of salicylic acid observed was 24 ng/mL and the estimated relative infant dose was 0.4%. Acetylsalicylic acid transfer to milk is so low that it is undetectable even by highly sophisticated methodology. Salicylic acid does appear in the human milk in comparatively low amounts, which are probably subclinical in infants. In one patient consuming 325 mg/day of aspirin, human milk levels of ASA were comparable with those taking 81 mg, or were undetectable (<0.61 ng/mL). In this patient, the maximum concentration of SA was observed as 744.6 ng/mL, which peaked at 1 hour. The area under the curve was 2579 ng.hr/mL and the average concentration estimated was 107.4 ng/mL. The relative infant dose calculated was 0.45% at this dose. Thus, the daily use of an 81-mg dose or 325 mg/day of aspirin should be considered safe during lactation.

While the direct use of ASA in infants and children has been associated with Reye syndrome, the use of the 81 mg/day dose, or even a single 325 mg dose, in breastfeeding mothers has not been linked to an increased risk of this syndrome in the infant. Unfortunately, we do not presently know of any specific dose-response relationship between aspirin and Reye syndrome other than in older children where even low plasma levels of ASA were implicated in Reye syndrome during viral infections such as flu or chickenpox. Lastly, acetylsalicylic acid is rapidly metabolized to salicylic acid by the liver and no ASA apparently reaches the plasma compartment, hence from the latter study, none is present in milk. Unusually large oral doses could change the outcome of the latter study and produce higher levels in plasma. This is unknown at this time.

Consider ibuprofen or acetaminophen as better choices for pain relief in lactating women. Avoid this medication at higher doses in lactation when the infant has a viral syndrome.

T 1/2	3-10 h	MW	180 Da	PB	88%-93%
Tmax	1-2 h	RID	2.5%-10.8%	Vd	0.15 L/kg
Oral	50%-75%	M/P	0.03-0.08	pKa	

Adult Concerns: Dizziness, confusion, tinnitus, Reye's syndrome, arrhythmias, dyspepsia, vomiting, stomach pain, gastrointestinal ulcers, changes in liver and kidney function, anemia, platelet dysfunction, increased risk of bleeding.

Adult Dose: 81 mg once daily; 325-650 mg q 4-6 hours (max 4 g/day).

Pediatric Concerns: One 16-day-old infant developed metabolic acidosis. Mother was consuming 3.9 g/day of ASA. Thrombocytopenia, petechiae, and anorexia were reported in an infant of 5 months following exposure to maternal milk containing aspirin. ASA has been associated with Reye syndrome in infants with viral fevers.

Infant Monitoring: Rare bruising on the skin, blood in urine or stool.

Alternatives: Ibuprofen(L1), Acetaminophen(L1).

References:

1. Pharmaceutical manufacturers prescribing information.
2. Findlay JW, DeAngelis RL, Kearney MF, Welch RM, Findlay JM. Analgesic drugs in breast milk and plasma. Clin Pharmacol Ther. 1981;29(5):625-633.
3. Erickson SH, Oppenheim GL. Aspirin in breast milk. J Fam Pract. 1979;8(1):189-190.
4. Bailey DN, Welbert RT, Naylor A. A study of salicylate and caffeine excretion in the breast milk of two nursing mothers. J Anal Toxicol. 1982;6:64-68.
5. Putter J, Satravaha P, Stockhausen H. Quantitative analysis of the main metabolites of acetylsalicylic acid. Comparative analysis in the blood and milk of lactating women. Z Geburtshilfe Perinatol. 1974;178:135-138.
6. Datta P, Rewers-Felkins K, Kallem RR, Baker T, Hale TW. Transfer of low dose aspirin into human milk. J Hum Lact. May 2017;33(2):296-299. doi:10.1177/0890334417695207. Epub March 20, 2017. PMID: 28418802.

ACITRETIN

Trade: Soriatane

Category: Antipsoriatic

LRC: L5 - Limited Data-Hazardous

Acitretin is used in the treatment of severe psoriasis. Its exact mechanism of action is unknown, but it helps to normalize cell differentiation and thin the cornified layer of the skin by reducing the rate of proliferation.[1] This product produces major human fetal anomalies and is retained in the body for long periods of time. Chronic use in breastfeeding mothers is probably not recommended. In the only study conducted on the transfer of acitretin into human milk, a 31-year-old mother was taking 40 mg once daily and had milk concentrations of 30-40 µg/L. This indicated that an infant would receive only 0.8% to 1.8% of the maternal dose; however, due to the toxic potential of this medication, the authors concluded that acitretin should be avoided during breastfeeding.[2]

T 1/2	49 h	MW	326 Da	PB	>99.9%
Tmax	2-5 h	RID	0.79%-1.8%	Vd	
Oral	72%	M/P		pKa	

Adult Concerns: Alopecia, headache, hyperesthesia, fatigue, xerophthalmia, xerostomia, cheilitis, hypercholesterolemia, hypertriglyceridemia, changes in liver function, increased WBC, arthralgias, skin peeling.

Adult Dose: 25-50 mg/day.

Pediatric Concerns: No data are available.

Infant Monitoring: Signs of jaundice—yellowing of the eyes and skin, skin rash.

Alternatives:

References:

1. Pharmaceutical manufacturers prescribing information.
2. Rollman O, Pihl-Lundin I. Acitretin excretion into human breast milk. Acta Derm Venereol. 1990;70:487-490.

ACYCLOVIR

Trade: Aciclover, Acyclo-V, Aviraz, Zovirax, Zyclir

Category: Antiviral

LRC: L2 - Limited Data-Probably Compatible

Acyclovir is converted by herpes simplex and varicella zoster virus to acyclovir triphosphate which interferes with viral HSV DNA polymerase. It is currently cleared for use in HSV infections, Varicella-Zoster, and under certain instances such as Cytomegalovirus and Epstein-Barr infections. There is virtually no percutaneous absorption following topical application and plasma levels are undetectable. The pharmacokinetics in children is similar to adults. In neonates, the half-life is 3.8-4.1 hours, and in children one year and older it is 1.9-3.6 hours.

Acyclovir levels in breast milk are reported to be 0.6 to 4.1 times the maternal plasma levels.[1] Maximum ingested dose was calculated to be 1500 µg/day assuming 750 mL milk intake. This level produced no overt side effects in one infant. In a study by Meyer[2], a patient receiving 200 mg five times daily produced breast milk concentrations averaging 1.06 mg/L. Using these values, an infant would ingest less than 1 mg acyclovir daily. In another study, doses of 800 mg five times daily produced milk levels that ranged from 4.16 to 5.81 mg/L (total estimated infant ingestion per day = 0.73 mg/kg/day).[3] Topical therapy on lesions other than nipple is probably safe. But mothers with lesions on or close to the nipple should not breastfeed on that side. Toxicities associated with acyclovir are few and usually minor. Acyclovir therapy in neonates is common and produces few toxicities. Calculated intake by infant would be less than 0.87 mg/kg/day.

T 1/2	2.4 h	MW	225 Da	PB	9%-33%
Tmax	1.5-2 h	RID	1.09%-1.53%	Vd	0.8 L/kg
Oral	15%-30%	M/P	0.6-4.1	pKa	7.99

Adult Concerns: Nausea, vomiting, diarrhea, sore throat, edema, and skin rashes.

Adult Dose: 200-800 mg every 4-6 hours.

Pediatric Concerns: None reported via milk in several studies.

Infant Monitoring: Vomiting, diarrhea.

Alternatives: Valacyclovir(L2).

References:

1. Lau RJ, Emery MG, Galinsky RE. Unexpected accumulation of acyclovir in breast milk with estimation of infant exposure. Obstet Gynecol. 1987;69(3 pt 2):468-471.
2. Meyer LJ, de Miranda P, Sheth N, Spruance S. Acyclovir in human breast milk. Am J Obstet Gynecol. 1988;158(3 pt 1):586-588.
3. Taddio A, Klein J, Koren G. Acyclovir excretion in human breast milk. Ann Pharmacother. 1994;28(5):585-587.

ADALIMUMAB

Trade: Humira

Category: Antirheumatic

LRC: L3 - Limited Data-Probably Compatible

Adalimumab is a recombinant humanized IgG1 monoclonal antibody specific for human tumor necrosis factor (TNF).[1] TNF is implicated in the pain and destructive component of arthritis and other autoimmune syndromes. This product would be similar to others such as etanercept (Enbrel) and infliximab (Remicade).

Two infants of women who took adalimumab 40 mg subcutaneously during lactation were followed until 14.5 and 15 months of age.[2] The first infant was exposed to adalimumab in pregnancy and lactation; the last dose was given 3.5 weeks before delivery. The maternal and infant serum levels on postpartum day 1 were 4900 ng/mL and 8400 ng/mL. Maternal serum and breast milk levels were taken again, this time they were drawn 7 days after an injection (about 21 weeks postpartum) and were found to be 6700 ng/mL and 4.83 ng/mL. In the second case, maternal serum and breast milk levels were drawn 9 days after the last injection (at about 8 weeks postpartum) and were found to be 5500 ng/mL and 4.88 ng/mL; in this case the infant's serum level was undetectable. No adverse reactions were found in the infant to be attributed to exposure of the drug in breast milk. Both infants were reported to have met all developmental milestones. One infant did develop acute spasmodic laryngitis at 10 months of age; however, this is a common disease among infants and was not deemed to be drug related by the authors of these case reports. The authors of this study postulated that immunoglobulins such as adalimumab might be absorbed via the immunoglobulin G-transporting neonatal Fc receptor (FcRn) that is expressed in intestinal cells of adults and fetuses.

Results from the PIANO registry study of 824 breastfeeding women with IBD who were taking biologic therapies were published in 2018. Twenty-one of these women reported taking adalimumab.[3] Two of the 21 had detectable levels of the drug peaking 12-24 hours after infusion (range 0.45-0.71 µg/mL, LOQ unknown). None of 7 women who submitted samples 1 week after the infusion had detective drug concentrations. All 824 babies exposed to immunomodulators or biologics in this study had similar rates of infections, reduced growth, or miss developmental milestones than unexposed infants throughout the 12-month duration of the study.

Although the molecular weight of this medication is very large and the amount in breast milk is very low, there is limited long-term data concerning the safety of using immune modulating medications in breastfeeding mothers. Further there are current data that suggest that some IgG drugs do transfer into milk, and perhaps the breastfed infant. Therefore, some caution is recommended, and each woman should understand the benefits and risk of using this type of medication in lactation.

T 1/2	2 weeks	MW	148,000 Da	PB	Nil
Tmax	131 h	RID	0.12%	Vd	4.7-6 L/kg
Oral	Low	M/P		pKa	

Adult Concerns: Headache, hypertension, nausea, changes in liver function, hematuria, hyperlipidemia, hypercholesterolemia, development of antibodies, infection, injection site reactions, and malignancies have been reported.

Adult Dose: 40 mg every other week subcutaneously.

Pediatric Concerns: None reported via milk.

Infant Monitoring: Vomiting, weight gain, frequent infections.

Alternatives: Infliximab(L3).

References:

1. Pharmaceutical manufacturers prescribing information.
2. Fritzsche J, Pilch A, Mury D, Schaefer C, Weber-Schoendorfer C. Infliximab and adalimumab use during breastfeeding. J Clin Gastroenterol. 2012;46(8):718-719.
3. Matro R, Martin CF, Wolf D, Shah SA, Mahadevan U. Exposure concentrations of infants breastfed by women receiving biologic therapies for inflammatory bowel diseases and effects of breastfeeding on infections and development. Gastroenterology. 2018;155(3):696-704.

ADAPALENE

Trade: Differin

Category: Antiacne

LRC: L3 - No Data-Probably Compatible

Adapalene is a retinoid-like compound (similar to Tretinoin) used topically for treatment of acne. No data are available on its transfer to human milk. However, adapalene is virtually unabsorbed when applied topically to the skin.[1] Plasma levels are almost undetectable (<0.25 mg/mL plasma), so milk levels would be infinitesimally low and probably undetectable.

T 1/2	17 h	MW	412.52 Da	PB	
Tmax		RID		Vd	
Oral	Very low	M/P		pKa	

Adult Concerns: Exacerbation of sunburn, irritation of skin, erythema, dryness, scaling, burning, itching.

Adult Dose: Apply topical daily.

Pediatric Concerns: None reported via milk. Very unlikely due to minimal maternal absorption.

Infant Monitoring:

Alternatives: Tretinoin.

References:

1. Pharmaceutical manufacturers prescribing information.

ADEFOVIR

Trade: Hepsera

Category: Antiviral

LRC: L4 - No Data-Possibly Hazardous

Adefovir inhibits hepatitis B virus replication.[1] No data are available on the transfer of adefovir into human milk. Based on the kinetic profile (low protein binding and moderate oral bioavailability), it is possible that the drug would enter the milk compartment to some degree. Because this drug is potentially toxic to a rapidly growing infant, and because it is used over long periods of time, it is not recommended for use in lactating mothers at this time.

T 1/2	7.5 h	MW	501 Da	PB	<4%
Tmax	1.75 h	RID		Vd	0.4 L/kg
Oral	59%	M/P		pKa	

Adult Concerns: Headache, abdominal pain, vomiting, changes in renal function, hematuria, weakness, rash.

Adult Dose: 10 mg daily.

Pediatric Concerns: No data are available at this time.

Infant Monitoring: Breastfeeding is not recommended in mothers who have HIV.

Alternatives: Lamivudine(L5).

References:

1. Pharmaceutical manufacturers prescribing information.

ADENOSINE

Trade: Adenocard, Adenoscan

Category: Antiarrhythmic

LRC: L2 - No Data-Probably Compatible

Adenosine produces a direct negative chronotropic, dromotropic, and inotropic effect on the heart, presumably due to A1-receptor stimulation, and produces peripheral vasodilation, presumably due to A2-receptor stimulation. The net effect of adenosine in humans is typically a mild to moderate reduction in systolic, diastolic, and mean arterial blood pressure associated with a reflex increase in heart rate. Rarely, significant hypotension and tachycardia have

been observed. There are no adequate well-controlled studies in breastfeeding.[1] However, adenosine has a half-life <10 seconds and is not likely in the systemic circulation long enough to enter milk. Based on this information, it is probably safe to use in breastfeeding.

T 1/2		MW	267.2 Da	PB	
Tmax		RID		Vd	
Oral	Nil	M/P		pKa	

Adult Concerns: Flushing, chest discomfort, dyspnea or urge to breathe deeply, headache, throat, neck or jaw discomfort, gastrointestinal discomfort, lightheadedness/dizziness.

Adult Dose: 6-12 mg.

Pediatric Concerns:

Infant Monitoring: Drowsiness, lethargy, pallor, arrhythmias, poor feeding, weight gain.

Alternatives:

References:

1. Pharmaceutical manufacturers prescribing information.

AFLIBERCEPT

Trade: Eylea, Zaltrap

Category: vascular endothelial growth factor (VEGF) inhibitor

LRC: L3 - No Data-Probably Compatible

Aflibercept is a recombinant fusion protein (115,000 Daltons) that acts as a vascular endothelial growth factor inhibitor used in the treatment of various retinal degenerations. Aflibercept binds to the VEGF-A and PIGF receptors and acts as a decoy. Injected intravitreally, it is unlikely to attain significant plasma levels, and what is present in the plasma is inactive and is undetectable two weeks postdosing. This product is unlikely to enter the milk compartment, and would not be orally bioavailable in a human.

T 1/2	5-6 days	MW	115,000 Da	PB	N/A
Tmax	1-3 days	RID		Vd	0.086 L/kg
Oral	N/A	M/P		pKa	N/A

Adult Concerns: Conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, increased intraocular pressure, ocular hyperemia, corneal epithelium defect, detachment of the retina.

Adult Dose: Variable

Pediatric Concerns:

Infant Monitoring:

Alternatives:

References:

1. Pharmaceutical manufacturers prescribing information.

ALBENDAZOLE

Trade: Albenza, Eskazole, Zentel

Category: Anthelmintic

LRC: L2 - Limited Data-Probably Compatible

Albendazole is a broad-spectrum anthelmintic used to treat intestinal parasite infections.[1] It is a pro-drug that is rapidly metabolized by the liver to an active metabolite, albendazole sulfoxide; albendazole sulfoxide is then metabolized to its inactive form albendazole sulphone. In a study of 33 breastfeeding women given a single 400 mg dose of albendazole, the maternal serum samples at 6 hours of albendazole (ABZ), albendazole sulfoxide (ABSX) and albendazole sulphone (ABSO) were 63.7, 608 and 100.7 ng/mL, respectively.[2]

The levels of ABZ in milk were 31.9, 18.8, 7.5 ng/mL, and undetectable at 6, 12, 24, and 36 hours. The levels of ABSX in milk were 312.8, 225.2, 94.1 and 57.1 ng/mL at 6, 12, 24, and 36 hours. The levels of ABSO were 52, 56, 19.9 ng/mL, and undetectable at 6, 12, 24, and 36 hours. The milk/serum ratios for ABZ, ABSX and ABSO

were 0.9, 0.6, and 0.7. Breast milk was withheld from the participants' infants (aged 2 weeks to 6 months) in this study. The authors suggest exposure to an infant via milk would be minimal. We calculated the RIDs (using the peak concentration for each component) to be: ABZ 0.08%, ABSX 0.82%, and ABSO 0.15%.

T 1/2	8-12 h	MW	265 Da	PB	70%
Tmax	2-5 h	RID	0.08%-0.82%	Vd	
Oral	Poor	M/P	0.6	pKa	

Adult Concerns: Headache, dizziness, fever, nausea, vomiting, abdominal pain, changes in liver function, pancytopenia, rash.

Adult Dose: 400 mg once to twice daily for 1-3 days (dosing varies by parasite).

Pediatric Concerns: No data are available for infant exposure via breast milk. Milk levels are unlikely to be clinically relevant. Commonly used in infants and children.

Infant Monitoring:

Alternatives: Mebendazole(L3).

References:

1. Pharmaceutical manufacturers prescribing information.
2. Abdel-Tawab AM, Bradley M, Ghazaly EA, Horton J, el-Setouhy M. Albendazole and its metabolites in the breast milk of lactating women following a single oral dose of albendazole. Br J Clin Pharmacol. 2009;68(5):737-742.

ALBUTEROL

Trade: Asmavent, Asmol, Proventil, Respax, Respolin, Salamol, Salbulin, Salbuvent, Ventolin

Category: Antiasthma

LRC: L1 - No Data-Compatible

Albuterol is a very popular beta-2 adrenergic agonist that is typically used to dilate constricted bronchi in asthmatics.[1] It is active orally but is most commonly used via inhalation. When used orally, significant plasma levels are attained, and transfer to breast milk is possible. When used via inhalation, less than 10% is absorbed into maternal plasma. Small amounts are probably secreted into milk, although no reports exist. It is very unlikely that pharmacologic doses will be transferred to the infant via milk following inhaler use. However, when used orally, breast milk levels could be sufficient to produce tremors and agitation in infants. Commonly used via inhalation in treating pediatric asthma. This product is safe to use in breastfeeding mothers.

T 1/2	3.8 h	MW	239 Da	PB	36%-93%
Tmax	5-30 min.	RID		Vd	2.2 L/kg
Oral	100%	M/P		pKa	10.3

Adult Concerns: Headache, dizziness, insomnia, hypertension, tachycardia, angina, dry mouth, hyperglycemia, hypokalemia, tremor.

Adult Dose: 2-4 mg TID or QID.

Pediatric Concerns: None reported via milk. Observe infant for tremors and excitement.

Infant Monitoring: Irritability, insomnia, arrhythmias, weight loss, tremor.

References:

1. Pharmaceutical manufacturers prescribing information.

ALCAFTADINE OPHTHALMIC SOLUTION

Trade: Lastacaft

Category: Antihistamine

LRC: L3 - No Data-Probably Compatible

Alcaftadine is an H1 histamine receptor antagonist used for allergic conjunctivitis. Following bilateral topical ocular administration of alcaftadine ophthalmic solution, 0.25%, the mean plasma C_{max} of alcaftadine was approximately 60 pg/mL and the median T_{max} occurred at 15 minutes. Plasma concentrations of alcaftadine were below the lower limit of quantification (10 pg/mL) by 3 hours after dosing. The mean C_{max} of the active carboxylic acid metabolite