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REVIEW ARTICLE

EXCRETION OF DRUGS THROUGH BREAST MILK

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ABSTRACT

Breastfeeding is the optimal form of infant feeding for the first months of an infant's life, and the majority of healthy women initiate breastfeeding after the birth of their infant. Although the majority of medications are considered to be compatible with breastfeeding, cases of significant infant toxicity exist, suggesting a case by case risk assessment to be made before the mother initiates breastfeeding or drug therapy. Unfortunately, current clinical risk assessment is often compromised by the paucity of data, as studies in breastfeeding women and their infants are ethically difficult to conduct. However, as our understanding on drug transfer mechanisms increases, it has become abundantly clear that carrier-mediated processes are involved with excretion of a number of drugs into milk. A common reason for the cessation of breastfeeding is the use of medication by the nursing mother and advice by her physician to stop nursing. Such advice may not be warranted. This information is important not only to protect nursing infants from untoward effects of maternal medication but also to allow effective pharmacologic treatment of breastfeeding mothers. The distribution of these drugs between the slightly more acidic breast milk and the relatively neutral plasma is consistent with their weakly basic, acidic, or relatively neutral properties. In general, the study shows that codeine and morphine milk concentrations are higher than, salicylic acid milk levels are much lower than, and phenacetin, caffeine, and acetaminophen milk concentrations are relatively similar to their respective plasma levels. It is projected, from estimated steady-state milk concentrations of the drugs and their metabolites studied, that very low percentages of the therapeutic dosages (less than 0.7%) would be excreted in mother's milk, too low an amount to be clinically significant to the infant. This article provides an overview of the benefits of breastfeeding, the effect of medication use during breastfeeding on maternal decisions and infant health, and factors determining infant exposure to medication through the breast milk.

Key Words: *Breastfeeding, infant feeding, infant toxicity, risk assessment, drug therapy.*

SUMMARY

INTRODUCTION

Excretion is defined as the process whereby drugs or metabolites are irreversibly transferred from internal to external environment through renal or non renal route. Excretion of unchanged or intact drug is needed in termination of its pharmacological action. The principal organ of excretion is kidneys.

TYPES OF EXCRETION

1. **RENAL EXCRETION**

2. **NON RENAL EXCRETION**
   - Biliary excretion.
   - Pulmonary excretion.
   - Salivary excretion.
   - Mammary excretion.
   - Skin / Dermal excretion.
   - Gastrointestinal excretion.
   - Genital excretion.

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BIOLOGICAL FACTORS: Age, sex, species, strain difference etc alter the excretion of the drug.

- **Sex –** Renal excretion is 10% lower in female than in males.
- **Age –** The renal excretion in newborn is 30-40 % less in comparison to adults.
- **Old age –** The GFR is reduced and tubular function is altered which results in slow excretion of drugs and prolonged half lives.

1) RENAL EXCRETION:

- **RENAL DYSFUNCTION**

Greatly impairs the elimination of drugs especially those that are primarily excreted by kidney. Some of the causes of renal failure are B.P, Diabetes, Pyelonephritis.

- **UREMIA**

Characterized by Impaired GFR, accumulation of fluids & protein metabolites, also impairs the excretion of the drugs. Half life is increased resulting in drug accumulation and increased toxicity.

2) NON-RENAL EXCRETION:

- **BILIARY EXCRETION**

  Bile juice is secreted by hepatic cells of the liver. The flow is steady-0.5 to 1ml /min. Its important in the digestion and absorption of fats.90% of bile acid is reabsorbed from intestine and transported back to the liver for resecretion. Compounds excreted by this route are sodium, potassium, glucose, bilirubin, Glucuronide, sucrose, Inulin, muco-proteins e.t.c., Greater the polarity better the excretion. The metabolites are more excreted in bile than parent drugs due to increased polarity.

- **PULMONARY EXCRETION**

  Gaseous and volatile substances such as general anesthetics (Halothane) are absorbed through lungs by simple diffusion. Pulmonary blood flow, rate of respiration and solubility of substance effect PE. Intact gaseous drugs are excreted but not metabolites. Alcohol which has high solubility in blood and tissues are excreted slowly by lungs.

- **SALIVARY EXCRETION**

  The pH of saliva varies from 5.8 to 8.4. Unionized lipid soluble drugs are excreted passively. The bitter after taste in the mouth of a patient is indication of drug excreted. Some basic drugs inhibit saliva secretion and are responsible for mouth dryness. Compounds excreted in saliva are Caffeine, Phenytoin, Theophylline.

- **MAMMARY EXCRETION**

  Milk consists of lactic secretions which is rich in fats and proteins. 0.5 to one liter of milk is secreted per day in lactating mothers. Excretion of drug in milk is important as it gains entry in breast feeding infants. PH of milk varies from 6.4 to 7.6.Free un-ionized and lipid soluble drugs diffuse passively. Highly plasma bound drug like Diazepam is less secreted in milk. Since milk contains proteins. Drugs excreted can bind to it.

- **MAMMARY EXCRETION**

  Amount of drug excreted in milk is less than 1% and fraction consumed by infant is too less to produce toxic effects. Some potent drugs like barbiturates and morphine may induce toxicity.

- **ADVERSE EFFECTS**

  Discoloration of teeth with tetracycline and jaundice due to interaction of bilirubin with sulfonamides. Nicotine is secreted in the milk of mothers who smoke.

- **SKIN EXCRETION**

  Drugs excreted through skin via sweat follows pH partition hypothesis. Excretion of drugs through skin may lead to urticaria and dermatitis. Compounds like benzoic acid, salicylic acid, alcohol and heavy metals like lead, mercury and arsenic are excreted in sweat.

- **GASTROINTESTINAL EXCRETION**

  Excretion of drugs through GIT usually occurs after parenteral administration. Water soluble and ionized from of weakly acidic and basic drugs are excreted in GIT. Example is nicotine and quinine are excreted in stomach. Drugs excreted in GIT are reabsorbed into systemic circulation & undergo recycling.

BREASTFEEDING:

- Healthcare professionals should always encourage breastfeeding
- Most drugs excreted into breast milk but usually in small amounts

- Few drugs are absolutely contra-indicated
- Some drugs may increase or decrease milk yield.

ADVANTAGES OF BREASTFEEDING:

- Reduced risk of fracture/osteoporosis
- Reduced risk of cancer
- Emotional
- Convenience
  Cost
  Baby
- Reduced risk of infection
- Reduced risk of SIDS
- Reduced risk of many immune mediated diseases
- Emotional/Bonding.

DRUG THERAPY OF THE LACTATING WOMAN:

The following should be considered before prescribing drugs to lactating women:

1. Is drug therapy really necessary? If drugs are required, consultation between the pediatrician and the mother's physician can be most useful in determining what options to choose.
2. The safest drug should be chosen, for example, acetaminophen rather than aspirin for analgesia.
3. If there is a possibility that a drug may present a risk to the infant, consideration should be given to measurement of blood concentrations in the nursing infant.
4. Drug exposure to the nursing infant may be minimized by having the mother take the medication just after she has breastfed the infant or just before the infant is due to have a lengthy sleep period.

DRUG SAFETY IN LACTATION – FACTORS TO BE CONSIDER

- Avoid unnecessary drug use and limit use of OTC products
- Assess the benefit/risk ratio for both mother and infant
- Avoid use of drugs known to cause serious toxicity in adults or children
- Drugs licensed for use in infants do not generally pose a hazard
- Neonates (premature infants) are at greater risk from exposure to drugs via breast milk
- Route of administration (minimum amount of drug to the infant)
- Avoid long-acting preparations
- Monitor Infants exposed to drugs via breast milk for unusual signs/symptoms
- Avoid new drugs if possible.

CHOICE OF DRUG– FACTORS TO BE CONSIDER

- Short acting
- Highly protein bound
- Low lipid solubility
- High molecular weight
- No active metabolites
- Low oral bioavailability
- Route of administration.

MECHANISM FOR DRUG PASSAGE THROUGH THE BREAST MILK:

1. The epithelium of the breast milk alveolar cells is most permeable to drugs during the first week post-partum, so drug transfer to milk may be greater during the first week of an infant's life.
2. Drug excretion into the milk depends on a number of factors related to the drug including
   a. Ionization of the drug - Drugs that are not protein bound and nonionized are more likely to be transferred into breast milk.
   b. Molecular weight of the drug - Lower molecular weight drugs are more likely to be transferred to the breast milk than higher molecular weight drugs.
   c. Solubility of the drug in lipids and waters - Lipid soluble drugs pass more freely into breast milk than water soluble drugs.
   d. The pH of the plasma and the milk - Weakly alkaline drugs have higher breast milk levels than weak acids.

3. Once the drugs have reached the alveolar cells of the breast they may then be transferred into the milk by:
   a. **Diffusion**: the movement of the drug from a high concentration area (blood) to a low concentration area (breast milk).
   b. **Active transport**: the movement of the drug from blood with a low concentration to breast milk with a high concentration. This mechanism concentrates the drug in the breast milk.

After diffusion or active transport, drugs pass through spaces between alveolar cells into the milk.

4. Most ingested drugs that appear in the milk do not exceed 2% of the ingested dose and the binding of the drug to milk proteins is less than the binding to plasma proteins.

BREASTFEEDING AND SMOKING:

The reasons for placing nicotine thus, smoking in were documented decrease in milk production and weight gain in the infant of the smoking mother and exposure of the infant to environmental tobacco smoke as demonstrated by the presence of nicotine and its primary metabolite, nicotinine, in human milk. There is controversy regarding the effects of nicotine on infant size at 1 year of age. There are hundreds of compounds in tobacco smoke; however, nicotine and its metabolite acotinine are most often used as markers of tobacco exposure. Nicotine is present in milk in concentrations between 1.5 and 3.0 times the simultaneous maternal plasma concentration, and elimination half-life is similar—60 to 90 minutes in milk and plasma. There is no evidence to document whether this amount of nicotine presents a health risk to the nursing infant. Pregnancy and lactation are ideal occasions for physicians to urge cessation of smoking. One study reported that, among women who continue to smoke throughout breastfeeding, the incidence of acute respiratory illness is decreased among their infants, compared with infants of smoking mothers who are bottle fed. It may be that breastfeeding and smoking is less detrimental to the child than bottle feeding and smoking.

SILICONE BREAST IMPLANTS AND BREASTFEEDING:

Approximately 800 000 to 1 million women in the United States have received breast implants containing silicone (elemental silicon with chemical bonds to oxygen) in the implant envelope or in the envelope and the interior gel. Concern has been raised about the possible effects to the nursing infant if mothers with implants breastfeed. This concern was initially raised in reports that described esophageal dysfunction in 11 children whose mothers had implants. Silicone chemistry is extremely complex; the polymer involved in the covering and the interior of the breast implant consists of a polymer of alternating silicon and oxygen atoms with methyl groups attached to the oxygen groups (methyl poly dimethyl siloxane). The length of the polymer determines whether it is a solid, gel, or liquid. There are only a few instances of the polymer being assayed in the milk of women with implants; the concentrations are not elevated over control samples. There is no evidence at the present time that this polymer is directly toxic to human tissues; however, concern also exists that toxicity may be mediated through an immunologic mechanism. There have been no other reports of clinical problems in infants of mothers with silicone breast implants. It is unlikely that elemental silicon causes difficulty, because silicon is present in higher concentrations in cow milk and formula than in milk of humans with implants. The anticolic compound simethicone is a silicone and has a structure very similar to the methyl poly dimethyl siloxane in breast implants. Simethicone has been used for decades in America and Europe without any evidence of toxicity to infants.

Transfer of drugs into breast milk is influenced by protein binding, lipid solubility and ionization:

Nearly all drugs transfer into breast milk to some extent. Notable exceptions are heparin and insulin which are too large to cross biological membranes. The infant almost invariably receives no benefit from this form of exposure and is considered to be an 'innocent bystander'. Drug transfer from maternal plasma to milk is, with rare exceptions, by passive diffusion across biological membranes. Transfer is greatest in the presence of low maternal plasma protein binding and high lipid solubility. In addition, milk is slightly more acidic than plasma (pH of milk is approximately 7.2 and plasma is 7.4) allowing weakly basic drugs to transfer more readily into breast milk and become trapped secondary to ionisation. Milk composition varies within and between feeds and this may also affect transfer of drugs into breast milk. For example, milk at the end of a feed (hindmilk) contains considerably more fat than foremilk and may concentrate fat-soluble drugs.

Transfer of drugs into breast milk is most commonly described quantitatively using the milk to plasma (M/P) concentration ratio. The accuracy of this value is improved if it is based on the area under the concentration-time curves (AUC) of the drug in maternal milk and plasma (M/P_{AUC}).

Calculation of infant exposure to drugs can be used to help guide safe use:

The infant's dose (D_{infant}) received via milk can be calculated using the maternal plasma concentration ($C_{maternal}$), M/P_{AUC} ratio and the volume of milk ingested by the infant (V_{infant}):

D_{infant} (mg/kg/day) = $C_{maternal}$ (mg/L) x M/P_{AUC} x V_{infant} (L/kg/day)

The volume of milk ingested by infants is commonly estimated as 0.15L/kg/day. The infant dose (mg/kg) can then be expressed as a percentage of the maternal dose (mg/kg). An arbitrary cut-off of 10% has been selected as a guide to the safe use of drugs during lactation. Drugs such as lithium (infant dose as high as 80% of the weight-adjusted maternal dose) and amiodarone (infant dose up to 50%) should be avoided due to high infant exposure and potential for significant toxicity. For drugs with greater inherent toxicity such as cytotoxic agents, ergotamine, gold salts, immunosuppressives and isotretinoin, the cut-off of 10% is too high and breastfeeding is contraindicated.

As a general rule, maternal use of topical preparations such as creams, nasal sprays or inhalers would be expected to carry less risk to a breastfed infant than systemically administered drugs. This is due to lower maternal concentrations and therefore lower transfer into breast milk. However, the risk to the infant must be considered in relation to the toxicity of the drug used, the dosage regimen and the area of application. For example, use of corticosteroids nasal sprays or inhalers in standard doses would be considered compatible with breastfeeding.

Other factors to consider in conjunction with the infant's dose include the pharmacokinetics of the drug in the infant. Generally, drugs that are poorly absorbed or have high first-pass metabolism are less likely to be problematical during breastfeeding. For example, gentamicin is highly hydrophilic and is very poorly absorbed when administered orally. Should any gentamicin be ingested via breast milk, it is unlikely to be absorbed.

Infants have lower drug clearance than adults:
Drug clearance in the infant is a particularly important consideration and premature infants have a severely limited ability to clear drugs. Within a few days of delivery, term infants have glomerular filtration rates approximately one-third of adult values after adjusting for difference in body surface area, and premature infants have even more impaired clearance (see Table 1). Generally, adult glomerular filtration rates (adjusted for the difference in surface area) are attained by five to six months of age. Metabolic processes such as phase 1 oxidation and phase 2 glucuronidation are also impaired in the neonate. Drugs subject to high first-pass metabolism may have higher oral availability in premature or term infants due to impaired ability to metabolise on first-pass. Adult metabolic capacity is attained towards the latter part of the infant's first year of life. The following table is useful for estimating infant clearance.

Table - 1: Approximate clearance values at different ages

Post-conceptual age	Clearance of drug
24-28 weeks	5%
28-34 weeks	10%
34-40 weeks	33%
40-44 weeks	50%
44-68 weeks	66%
> 68 weeks	100%

Drugs affecting milk:

Drugs can affect milk secretion or composition by affecting factors such as mammary gland development, milk secretion and hormonal regulation of lactation. Prolactin is necessary for human milk secretion and may be affected by drug use. Dopamine agonists such as cabergoline reduce prolactin and are sometimes used therapeutically to stop lactation. Dopamine antagonists such as metoclopramide and most antipsychotics may increase prolactin (see article on Hyperprolactinaemia With Antipsychotics) and milk production. Other drugs that have been associated with causing hyperprolactinaemia include SSRIs and opioids.

Tabulated summary of drug distribution into breast milk:
Table 2 shows published M/P ratios from the literature and provides an estimate of the weight-adjusted infant dose. Interpretation of these requires an understanding of the limitations associated with published data, such as the availability of only single pairs of plasma and milk concentrations. Infant clearance (related to post-conceptual age) should always be considered.

Table - 2: Summary of distribution of drugs into breast milk

Drug	M/P_{AUC}	% maternal dose	Comments
Acid-suppressants:			
Cimetidine	1.7-5.8	5.4-6.7	Avoid in favour of safer alternatives with lower potential for side effects. May accumulate in milk due to active transport.
Famotidine	1.5	1.6	Probably safe.
Ranitidine	2.8	5.0-7.8	Probably safe when restricted to sporadic doses or a single dose at night-time. May accumulate in milk due to active transport.
Analgesics:			

Aspirin	0.06	3.2	Avoid due to possible association with Reye's syndrome.
Codeine	2.16	6.8	Considered safe.
Ibuprofen	0	< 0.6	Considered safe. Not detected in milk.
Indomethacin	0.37	< 1.0	Considered safe. One case of seizures (causality questionable).
Mefenamic acid	ID	0.3	Probably safe.
Methadone	0.47	2.2	Considered safe in methadone maintenance as 60% of infants born to mothers in maintenance programmes develop symptoms of withdrawal.
Morphine	2.46	0.4	Considered safe.
Naproxen	ID	1.1	Probably safe.
Nefopam	ID	0.4	Probably safe.
Piroxicam	ID	5-10	Use a NSAID with a shorter half-life where possible.
Paracetamol	0.8	2.9-7.9	Considered safe.
Sumatriptan	4.1-5.7	0.3-6.7	Exposure limited by low oral availability in term infants. Expressing for 8 hours post-dose will almost completely avoid exposure.
Antibiotics:			
Aminoglycosides			
Gentamicin	0.17	2.2	Considered compatible with breastfeeding due to low transfer and low oral availability.
Cephalosporins			Considered safe. Low transfer into milk. Third generation cephalosporins have greater potential to alter bowel flora.
Cefaclor	ID	0.7	
Cefalexin	0.09	0.5-1.2	
Cefotaxime	ID	0.3	
Ceftriaxone	0.04	0.7-4.7	
Fluoroquinolones			
Ciprofloxacin	2.17	4.8	Avoid fluoroquinolones due to theoretical risk of arthropathies.
Macrolides			Considered safe. May alter bowel flora.
Clarithromycin	0.25	1.8	
Erythromycin	0.41	2.1	
Penicillins			Considered safe. Note: although amoxycillin/clavulanic acid combination is used extensively in lactation, there are no published data on the safety of clavulanic acid.
Tetracyclines			Avoid tetracyclines where feasible due to the possible risks of dental staining and adverse effects on bone development.
Minocycline	ID	3.6	
Tetracycline	0.58	4.8	
Aciclovir	ID	1.1-1.2	Considered safe. No adverse effects noted in breastfed infants.
Fluconazole	0.75	11	Potential for accumulation particularly in premature infants.
Metronidazole	0.9-1.1	0.1-36.0	Controversial as exposure may be high. With high doses consider expressing and discarding milk.
Nitrofurantoin	ID	0.6-6.0	Avoid in G6PD-deficient infants (due to the risk of haemolysis).
Sulphamethoxazole & Trimethoprim (i.e. co-trimoxazole)	0.1 1.26	2-2.5 3.8-5.5	Avoid suphaemethoxazole in infants with hyperbilirubinaemia and G6PD deficiency.
Anticoagulants			
Warfarin	0	< 4.4	Probably safe. No changes in prothrombin times detected in breastfeeding infants. Monitor prothrombin time.
Anticonvulsants:			
Carbamazepine	0.36-0.39	2.8-7.3	Considered safe. Monitor for sedation, poor suckling.
Lamotrigine	ID	10-22	Concentrations in breastfed infants have been consistent with those expected to produce clinical effect. Best to avoid.

Phenobarbitone	ID	23-156	Avoid due to high infant exposure.
Pheyntoin	0.13-0.18	3.0-7.2	Considered safe. Observe for sedation, poor suckling. One report of methaemoglobinaemia, poor suckling and sedation.
Sodium valproate	0.05	1.8	Considered safe at low doses. High doses may increase the risk of hepatitis.
Vigabatrin	ID	<1%	Avoid until further data are available.
Antidepressants:			
Tricyclics:			Probably safe. Negligible or no concentrations detected in breastfed infants.
Amitriptyline	0.83	0.6-0.9	
Desipramine	ID	0.5-1.0	
Dothiepin	0.8-1.6	0.2-1.5	
Doxepin	ID	0.01	
Imipramine	ID	0.13	
Nortriptyline	ID	0.53	
SSRIs			
See text			
Others			
Moclobemide	0.72	1.6	Probably safe.
Antiemetics:			
Domperidone	ID	0.05	Probably safe. May increase milk secretion.
Metoclopramide	ID	4.7-11.3	Low dose or sporadic use probably safe. May increase milk secretion.
Antihistamines:			
Loratadine	1.2	0.7	Probably safe. No adverse effects reported in infants.
Triprolidine	0.53	0.9	Considered safe.
Antipsychotics:			Probably safe. May increase milk secretion. Monitor infant for sedation, irritability etc.
Chlorpromazine	ID	0.2	
Flupenthixol	ID	0.5-0.8	
Haloperidol	ID	0.15-2.0	
Cardiovascular:			
Amiodarone	ID	37	Avoid in breastfeeding.
Atenolol	2.3-4.5	5.7-19.2	Avoid in favour of antihypertensives with lower infant exposure.
Captopril	0.03	0.014	Considered safe.
Digoxin	0.6-0.9	2.3-5.6	Considered safe.
Diltiazem	0.98	0.9	Unlikely to be problematical in breastfeeding.
Enalapril	0.02	< 0.1	Considered safe.
Metoprolol	2.8-3.6	1.7-3.3	Probably safe.
Nadolol	4.6	5.1	Consider choosing a beta-blocker with a lower infant dose, if feasible.
Propranolol	0.32-0.76	0.2-0.9	Probably safe.
Quinapril	0.12	1.6	Considered safe.
Verapamil	0.6	0.14-0.84	Considered safe.
Sedatives/hypnotics:			
Clonazepam	ID	1.5-3.0	Short-term use of low doses is probably safe.
Diazepam	0.16	2.0-2.3	Reasonable to breastfeed after a low single dose but potential for accumulation with prolonged use. Sedation has been reported in breastfed infants.

Lorazepam	ID	2.2	Short-term use of low doses is probably safe.
Midazolam	0.16	0.7	Short-term use of low doses is probably safe.
Nitrazepam	ID	ID	Short-term use of low doses is probably safe. Potential for accumulation with prolonged administration.
Zopiclone	0.5	4.1	Short-term use of low doses is probably safe.
Social Drugs:			
Cannabis (THC)	ID	ID	Avoid as long-term effects are unknown.
Caffeine	0.5-0.8	0.6-21.0	Low intake probably safe. Restlessness and irritability documented. Prolonged half-life (80-100 hours) in neonates.
Ethanol	0.9	3-4	Occasional low usage probably safe. Chronic intake may be associated with impairment of psychomotor development. Consider withholding breastfeeding for 1-2 hours per standard drink.
Nicotine	2.92	ID	Cigarette smoking should be avoided due to health hazards associated with smoking. Use of nicotine patches may be considered compatible with breastfeeding and is favoured over smoking.
Miscellaneous:			
Ethinyloestradiol	ID	0.3	May suppress lactation.
Levonorgestrel	ID	1.1	Considered safe.
Medroxyprogesterone	ID-0.72	3.4-5.0	Considered safe.
Norethisterone	ID-0.26	0.02-1.9	Considered safe.
Prednisone	ID	0.26	Short courses of low doses (≤ 20mg daily) are probably safe. Note: there are insufficient data on other systemic corticosteroids (e.g. betamethasone, dexamethasone).
Pseudoephedrine	2.5	4.0	Low doses or sporadic use probably safe.
Sulphasalazine	ID	1.2-7.0	Avoid in infants with hyperbilirubinaemia or G6PD.

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CONCLUSION

With an ever-increasing number of drugs becoming available to an increasing number of women consumers, the topic of drug therapy and breast feeding is of the utmost practical importance. Unless information to the contrary exists, it can be assumed that almost all drugs administered to the mother will be excreted, to a certain extent, in the breast milk, and thus the breast-fed baby is an unintended recipient of the drugs administered to the mother. Drug excretion will be influenced by milk production, milk composition, pH of the milk, and blood flow to the breast tissue. Since drugs traverse membranes by passive diffusion, the final concentration will depend on the degree of ionization and protein binding of the particular drug molecule, and its molecular weight. Drugs that are weak bases will be present in breast milk at the same or higher concentrations than in plasma. Conversely, drugs that are weak acids will be present in breast milk at a much lower concentration than in the plasma. Certain principles should be followed when prescribing drugs during breast feeding or advising on breast feeding during drug therapy. The overall risk of a drug to a breastfed infant depends on the concentration in the infant's blood and the effects of the drug in the infant. If, after assessment of the risks and benefits, the decision is made to breastfeed while the mother is using a drug, the infant should be monitored for adverse effects such as failure to thrive, irritability and sedation. However, it is difficult to identify adverse reactions occurring in neonates. Feeding immediately prior to a dose may help to minimise infant exposure as concentrations in milk are likely to be lowest towards the end of a dosing interval. However, for some drugs, milk concentrations lag behind plasma concentrations.

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