

Drugs affecting breast milk and lactation

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Learning issues

Student should be able to :

- **Recognize the main pharmacological characters that control the passage of drugs from milk to baby.**
- **Identify the adverse effects of major pharmacological categories on babies.**
- **Describe the best and safest medication to be given to breast feeding women if she is suffered from different diseases as epilepsy, infection, diabetes, heart failure, hypertension.**
- **Know drugs that can inhibit lactation and should be avoided in breast feeding**
- **Know drugs that may enhance lactation.**

LACTATION

- ***Breast feeding*** is very important because breast milk is the healthiest form of milk for babies.
- It provides the baby with immunoglobulins (IgA, IgM) that are essential for protection against gastroenteritis.



DRUGS AND LACTATION

- **Most drugs administered to breast feeding woman are detectable in milk.**
- **The concentration of drugs achieved in breast milk is usually low (< 1 %).**
- **However, even small amounts of some drugs may be of significance for the suckling child.**
- **There are many pharmacokinetic and pharmacodynamics changes in pediatrics.**

Pediatric population are classified into:

- **Newborn:** less than one month old
 - **Preterm neonates:** born before 38 weeks of pregnancy
 - **Full-term neonates:** 38-42 weeks of gestational age
- **Infants (babies):** 1 month – 12 months of age
- **Children:** 1 -12 years of age
 - **Toddler (young child):** 1-5 years
 - **Older child:** 6-12 years
- **Adolescent:** 13-18 years

Pharmacokinetics changes in pediatrics

- Higher gastric pH
- Higher concentrations of free drug
- Higher percentage of body water
- Lower rate of metabolism due to immaturity of liver enzymes.
- Renal clearance is less efficient: (↓ Renal blood flow- ↓ GFR).
- **Premature babies** have very limited capacity for metabolism and excretion.

Physiologic Differences between Neonates and Adults of Pharmacokinetic Importance (Hilligoss 1980)

	Neonate	Adult
Gastric acid output (mEq/10kg/hr)	0.15 ↓	2
Gastric emptying time (min)	87 ↑	65
Total body water (% of body weight)	78 ↑	60
Adipose tissue (% of b.wt.)	12 ↓	12-25
Serum albumin (gm/dL)	3.7 ↓	4.5
Glomerular filtration rate (ml/min/m ²)	11 ↓	70

Factors controlling passage of drugs into breast milk

Factors related to drugs :

- Molecular weight
- Lipid solubility
- Degree of ionization
- Drug pH
- Protein binding
- Half life
- Oral bioavailability

Factors controlling passage of drugs into breast milk

Maternal factors:

- Dose of drug
- Route of administration
 - Time of breast feeding
 - Health status
 - Maternal drug concentration

Factors controlling passage of drugs into breast milk

Infants factors:

- Age
- Body weight
- Health status

Factors related to drugs

Molecular weight:

- Very small molecules (< 200 Daltons) such as **alcohol**, equilibrate rapidly between plasma and breast milk via the aqueous channels surrounding alveoli.
- Large molecules drugs (>800 Daltons) are less likely to be transferred to breast milk than low molecular weight.
- **Insulin:** MW > 6,000 daltons
- **Heparin:** MW 40,000 daltons

- Monoclonal antibodies, pass very poorly into milk after the first 1st week postpartum.
- The epithelium of the breast alveolar cells is most permeable to drugs during the 1st week postpartum, so drug transfer to milk may be greater during the 1st week of an infants life.

Lipid solubility of the drug:

Lipid soluble drugs pass more freely into the breast milk than water soluble drugs.

Degree of ionization:

- Ionized form of drugs are less likely to be transferred into breast milk.
- e.g., heparins pass poorly into breast milk

pH of drug:

- pH of milk is slightly more acidic than maternal blood.
- Weak basic drugs tend to concentrate in breast milk and become trapped secondary to ionization.
- **Weak acidic drugs** don't enter the milk to a significant extent and tend to be concentrated in plasma.

Effect of pH of the plasma and milk

Maternal blood circulation

plasma pH is 7.4

Milk

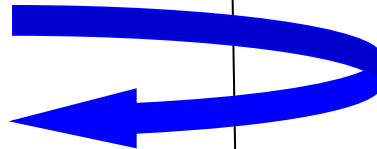
Milk pH is 7.2
More acidic

Alkaline drug



Ionized alkaline drug
will be captured

Acidic drug



Nonionized acidic drug
will diffuse back

Plasma protein binding of drugs

- Drugs circulate in maternal circulation in unbound (**free**) or bound forms to albumin.
- **Only** unbound form gets into maternal milk.
- Definition of good protein binding > 90%
- e.g. warfarin

Half life of drug

- Avoid the use of drugs with long half lives
- short half life ($t_{1/2}$) are preferable.
- Oxazepam *vs* diazepam

Volume of distribution

Transfer of drug from maternal blood to milk is low with drugs that have large volume of distribution (V_d).

Factors related to mother

- Dose of the drug
- Route of administration
- Time of breast feeding
- Health status
- Maternal drug concentration

Factors related to mother

Route of administration

- Route of administration affect the concentration of the drug in maternal blood.
- Maternal use of **topical preparations (creams, nasal sprays or inhalers)** are expected to carry less risk to a breastfed infant than systemically administered drugs.

Factors related to mother

Time of breastfeeding

- The **concentration** of the drug in the milk at the time of feeding.
- Lactating mother should take medication just **after nursing and 3-4 hours before the next feeding.**

(to allow time for drug to be cleared from the mother's blood – drug concentration in milk will be low).

Health status

Breastfeeding is contraindicated in case of:

- Mother HIV
- Active, untreated TB in mother
- Herpes on breast
- Use of illegal drugs by mother
- Certain medications

Factors related to neonates

- Age
- Body weight
- Health status

The amount of a drug to which the baby is exposed as a result of breast feeding depends on:

- The **amount** of milk consumed.
- The **amount** of drug absorbed from GI.
- The **ability** of the baby to eliminate the drug.

Age & Health status

Special cautions are required in

- Premature infants
- Low birth weight
- Infants with G6PD deficiency
- Infants with impaired ability to metabolize /excrete drugs e.g. hyperbilirubinemia.



Neonatal hyperbilirubinemia

Premature infants or infants with inherited G6PD deficiency are susceptible to **oxidizing drugs** that can cause \rightarrow hemolysis of RBCS $\rightarrow \uparrow$ bilirubin (hyperbilirubinemia) $\rightarrow \uparrow$ Kernicterus .

Examples for oxidizing drugs:

Antibiotics sulfonamides, trimethoprim

Antimalarials: Primaquine

Neonatal Methemoglobinemia

- Infants under 6 months of age are particularly prone to develop methemoglobinemia upon exposure to some oxidizing drugs.
- **Methemoglobin** is an oxidized form of hemoglobin that has a decreased affinity for oxygen → **tissue hypoxia.**

Drugs contraindicated during lactation

- Only few drugs are totally contraindicated
- **Anticancer drugs**
 - Doxorubicin, cyclophosphamide, methotrexate
- **Radiopharmaceuticals** e.g. radioactive iodine
- **CNS acting drugs** amphetamine, heroin, cocaine
- **Lithium**
- **Chloramphenicol**
- **Atenolol**
- **Potassium iodide**

Drugs that can suppress lactation

These drugs reduce prolactin

- **Levodopa** (dopamine precursor)
- **Bromocriptine** (dopamine agonist).
- **Estrogen, combined oral contraceptives that contain high-dose of estrogen and a progestin.**
- **Androgens**
- **Thiazide diuretics**

Drugs that can augment lactation

Dopamine antagonists :

they stimulate prolactin secretion galactorrhea

e.g.

- **Metoclopramide** (antiemetic)
- **Domperidone** (antiemetic)
- **Haloperidol** (antipsychotic)
- **Methyl dopa** (antihypertensive drug)
- **Theophylline** (used in asthma)

Antibiotics

Penicillins Ampicillin amoxicillin	No significant adverse effect allergic reactions, diarrhea
Cephalosporins	No significant adverse effect Alterations to infant bowel flora
Macrolides erythromycin clarithromycin	
Sulfonamides (co-trimoxazole)	hyperbilirubinemia -neonatal jaundice Should be avoided in premature infants or infants with G6PD deficiency

Antibiotics

Quinolones	Theoretical risk of arthropathies Should be avoided
Chloramphenicol	“Gray baby” syndrome avoid
Tetracyclines	Absorption by the baby is probably prevented by chelation with milk calcium. Avoid due to possible risk of teeth discoloration.
Sulfonamides (co-trimoxazole)	hyperbilirubinemia -neonatal jaundice Should be avoided in premature infants or infants with G6PD deficiency

Sedative/hypnotics

Barbiturates (phenobarbitone)	Lethargy, sedation, poor suck reflexes with prolonged use.
Benzodiazepines Diazepam Lorazepam	Single use of low doses is probably safe. Lethargy, sedation in infants with prolonged use.

Antidiabetics

Insulin

Oral antidiabetics

Metformin

safe

compatible

avoid due to lactic acidosis

Analgesics

Paracetamol

safe

Ibuopfen

compatible

Aspirin

avoid due to theoretical risk of
Reye's syndrome

Oral contraceptives

Non hormonal method should be used

Avoid estrogens containing pills

Estrogens ↓ milk quantity

Progestin only pills or minipills are preferred for birth control.

Antithyroid drugs

Propylthiouracil

Carbimazole

Methimazole

potassium iodide

May suppress thyroid function in infants.

Propylthiouracil should be used rather than carbimazole or methimazole.

Anticoagulants

Heparin

Safe, not present in breast milk.

Warfarin

Warfarin can be used, very small quantities found in breast milk, **monitor the infant's prothrombin time during treatment.**

Anticonvulsants

Carbamazepine

Phenytoin

Valproic acid

Lamotrigine

Preferable over others

Compatible with breastfeeding

Amounts entering breast milk are not sufficient to produce adverse effects

Infants must be monitored for CNS depression

avoid

Antidepressants

SSRI

Paroxetine is the preferred SSRI in breastfeeding women.

Cytotoxic drugs	Breast feeding should be avoided
Iodine (radioactive)	Permanent hypothyroidism in infant Breast-feeding is contraindicated
Lithium	Large amounts can be detected in milk avoid
CVS drugs Atenolol	Risk of bradycardia and hypoglycemia avoid

Drugs of choice in lactation

Antibiotics	Cephalosporins, penicillins are safe Avoid: chloramphenicol, quinolones, sulphonamides and tetracyclines
Antidiabetics	Insulin – oral antidiabetics are safe Avoid: metformin
Anticoagulants	Heparin – warfarin
Analgesics	Acetaminophen (paracetamol)
Antithyroid drugs	Propylthiouracil is preferable over others
Anticonvulsants	Carbamazepine - phenytoin
Oral contraceptives	Progestin only pills or minipills are preferred for birth control.
Antiasthmatics	Inhaled corticosteroids - prednisone

Summary for choice of drug

- **Route** of administration (**topical, local, inhalation**) instead of an oral form.
- **Short** acting
- **Highly** protein bound
- **Low** lipid solubility
- **High** molecular weight
- **Poor** oral bioavailability
- **No** active metabolites
- **well-studied** in infants

General considerations

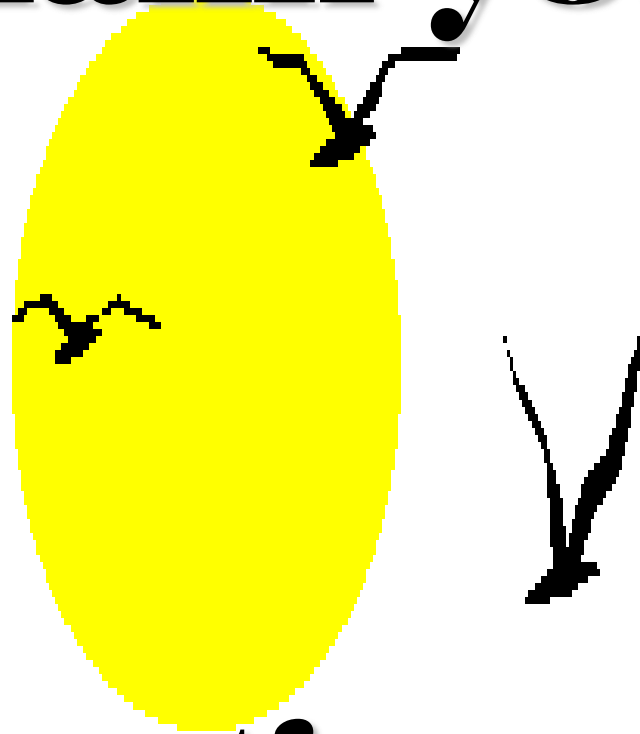
- Infants should be monitored for adverse effects e.g. feeding, sedation, irritability, rash, etc.
- Drugs with no safety data should be avoided or lactation should be discontinued

General considerations

- Do not guess
- Use the following sources:
 - Use Medication and Mothers' Milk
(www.iBreastfeeding.com)
 - Use lactmed or toxnet
(<http://toxnet.nlm.nih.gov>)

a free online database with information on drugs and lactation, is one of the newest additions to the National Library of Medicine's TOXNET system, a Web-based collection of resources covering toxicology, chemical safety, and environmental health.

Thank you



Questions ?