Drugs affecting breast milk and lactation

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Adapted from slides prepared by Dr. Hanan Hagar

Learning objectives

Student should be able to :

- Recognize the main pharmacological characteristics that control the passage of drugs to breast milk.
- Identify the adverse effects of major pharmacological categories on breast fed baby.
- Describe the best and safest medication during breast feeding in cases of epilepsy, infections , diabetes, heart failure, hypertension.
- Know drugs that can inhibit lactation
- 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

- Drugs ingested by the mother diffuse or are transported from the maternal plasma to the alveolar cells of the breast.
- The concentration of drugs detected in breast milk is usually low.
- However, even small amounts of some drugs may be of significance for the child.

DRUGS AND LACTATION

- Number of drugs are absolutely contraindicated.
- Some drugs may increase or decrease milk yield.

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: (decreased renal blood flow-decreased 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/m2)	11 ↓	70

Factors controlling passage of drugs into breast milk

A. 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

B. 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

C. Infants factors:

- Age
- Body weight
- Health status

A. Factors related to drugs

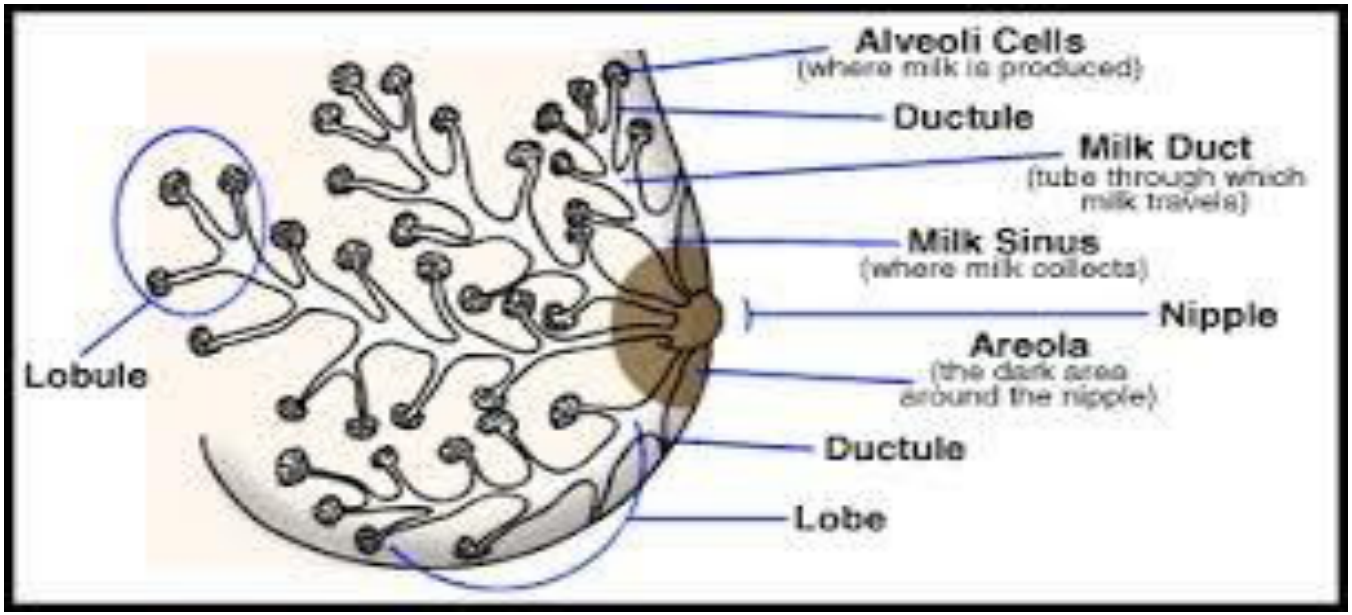
1. Molecular weight:

- 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
- 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.



2. Lipid solubility of the drug:

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

3. Degree of ionization:

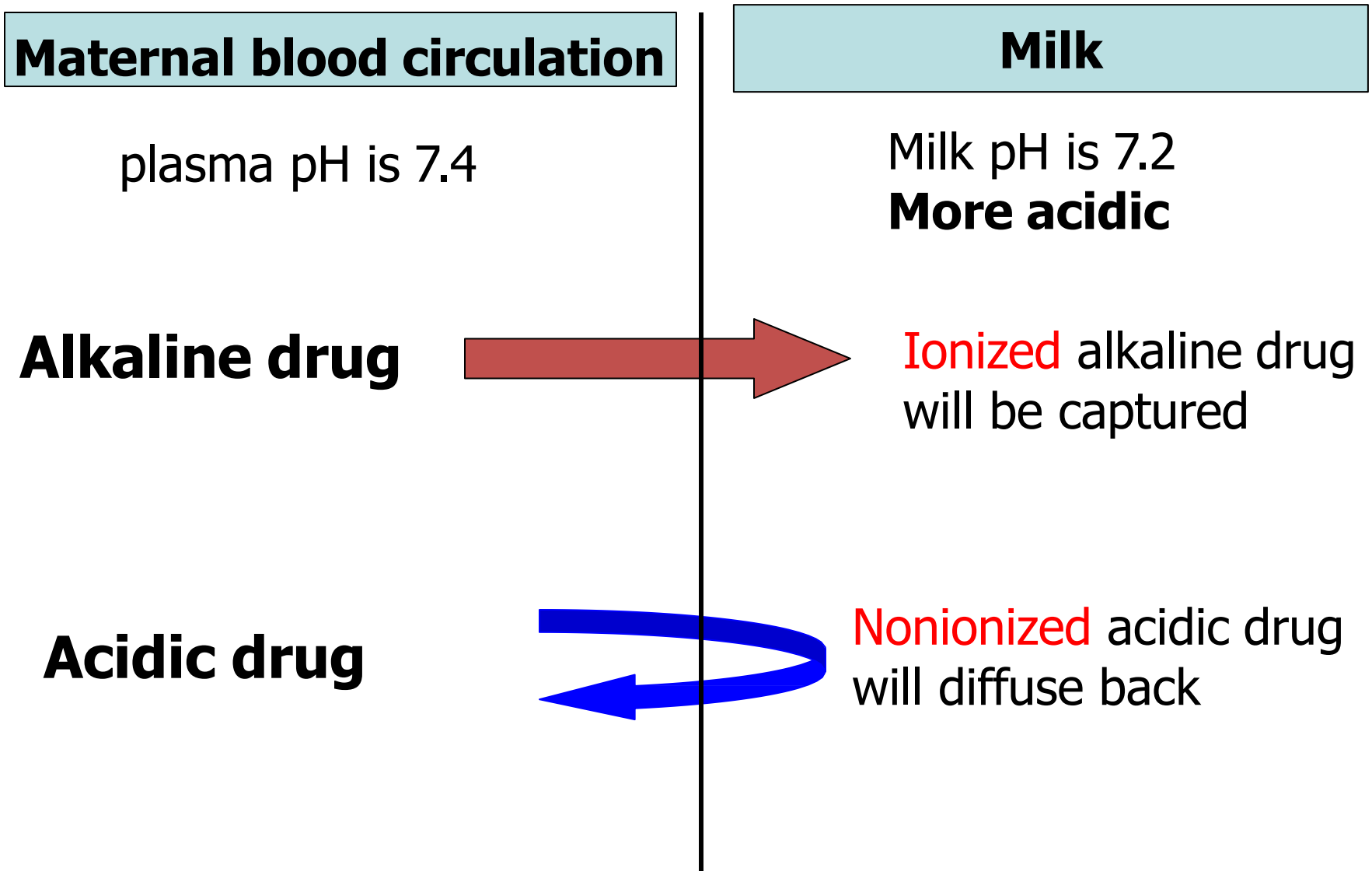
- Ionized form of drugs are less likely to be transferred into breast milk.
- e.g., heparins pass poorly into breast milk

4. 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



5. 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 is > 90% binding e.g. warfarin

6. Half life of drug

- Avoid the use of drugs with long half lives
- Short half life (t ½) are preferable.
- Oxazepam *vs* diazepam (short half life *vs* long half life)

7. Volume of distribution of drugs

Transfer of drugs from maternal blood to milk is

Low with drugs that have large volume of distribution

(Vd).

B. Factors related to mother

1. 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.

2. 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).

3. Health status

Breastfeeding is contraindicated in case of:

- HIV-positive women
- Active, untreated TB in mother
- Herpes on breast
- Use of illegal drugs by mother
- Certain medications used on a chronic basis.

C. Factors related to neonates

- Age
- Body weight
- Health status

Age & Health status

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 old
- Children: 1 -12 years old
- Adolescent: 13-18 years old

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 → hemolysis of RBCS →↑ bilirubin (hyperbilirubinemia) →↑ 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

- Several drugs are totally contraindicated
- **Anticancer drugs (**cytotoxicity & neutropenia)
  - Doxorubicin, Cyclophosphamide, Methotrexate
- **Radiopharmaceuticals**
  - e.g. Radioactive iodine
- **CNS acting drugs**
  - Amphetamine, Heroin, Cocaine
- **Immunosuppressants:**
  - Cyclosporine

- **Alcohol &Lithium** (high milk to plasma ratio)
- **Chloramphenicol (**bone marrow suppression)
- **Atenolol**
- **Potassium iodide (**thyroid effect)
- **Ergotamine** (for migraine headaches) causes (vomiting, diarrhea, convulsions in infants)
- **Tobacco Smoke**:
  - Nicotine can cause vomiting, diarrhea and restlessness for the baby, decreased milk production & increase the incidence of respiratory and ear infections.

Drugs that can suppress lactation

The more **dopamine**, the less **prolactin** is released.

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 increase lactation

Dopamine antagonists :

- Stimulate prolactin secretion and galactorrhea for examples:
  - Metoclopramide (antiemetic)
  - Domperidone (antiemetic)
  - Haloperidol (antipsychotic)
  - Methyl dopa (antihypertensive drug)
  - Theophylline (used in asthma)

Antibiotics

Penicillins Ampicillin amoxacillin	No significant adverse effect allergic reactions, diarrhea
Cephalosporins	No significant adverse effect Alterations to infant bowel flora
Macrolides erythromycin clarithromycin	

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	Safe
Oral antidiabetics	Compatible
Metformin	Avoid due to lactic acidosis

Analgesics

Paracetamol	Safe
Ibuoprofen	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 Warfarin	Safe, not present in breast milk. Warfarin can be used, very small quantities found in breast milk, monitor the infant's prothrombin time during treatment.

Anticonvulsants	Preferable over others
Carbamazepine	Compatible with breastfeeding
Phenytoin	Amounts entering breast milk are not sufficient to produce adverse effects
Valproic acid	Infants must be monitored for CNS depression, hepatotoxicity
Lamotrigine	**Avoid**
Antidepressants	
SSRI	Paroxetine is the preferred SSRI in breastfeeding women.

Antihistaminics	Sedating antihistaminics e.g. Diphenhydramine avoid	
	Non-sedating antihistaminics e.g. Loratidine Safe at lower doses	

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

- Drugs known to have serious toxic effects in adults are avoided
- Route of administration (topical, local, and inhalation) instead of an oral form.
- Drugs which are:
  - 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

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