Pharmacology
Team 437

Drugs Affecting Breast Milk & Lactation

Objectives:

1. Recognize the main pharmacological characters that control the passage of drugs from milk to baby.
2. Identify the adverse effects of major pharmacological categories on babies.
3. 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.
4. Know drugs that can inhibit lactation and should be avoided in breastfeeding
5. Know drugs that may enhance lactation.

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Color index:
Important Note Extra

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Lactation

- ✓ Breastfeeding 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 achieved in breast milk is usually low (< 1 %).
- ❖ However, even small amounts of some drugs may be of significance for the suckling child.
- ❖ Few drugs are absolutely contraindicated.
- ❖ Some drugs may increase or decrease milk yield.

Pharmacokinetics changes in pediatrics

- ❖ Premature babies have very **limited capacity for metabolism** and **excretion.**

So some drugs will get destroyed

Higher gastric pH

I'm a normally born baby

Higher concentration of free drug
Bc newborns have low protein-binding capacity → high free amounts

Higher percentage of body water
Water soluble drugs have higher volume of distribution

Lower rate of metabolism (due to immaturity of liver enzymes

Renal clearance is less efficient (reduced renal blood flow → ↓ GFR

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

	Neonate	Adult
Gastric acid output (mEq/10 kg/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

You don't have to memorize it

Factors Controlling Passage of Drugs Into Breast Milk

Factors related to <u>drugs</u>	<u>Maternal</u> factors	<u>Infant</u> factors
❖ **Molecular weight** ❖ **Lipid solubility** ❖ **Degree of ionization** ❖ **Drug pH** ❖ **Protein binding** ❖ **Half life** ❖ **Oral bioavailability**	❖ Dose of drug ❖ Route of administration ❖ Time of breastfeeding ❖ Health status ❖ Maternal drug concentration	❖ Age ❖ Body weight ❖ Health status

Factors Related to Drugs

1. Molecular Weight

Very small (<200 Daltons)

Equilibrate rapidly between plasma and breast milk via the aqueous channels surrounding alveoli

↠ E.g. alcohol
+ Lithium

Large (>800 Daltons)

less likely to be transferred to breast milk than low molecular weight.

↠ E.g. Insulin (>6,000 daltons).
Heparin (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 infant's life.

2. Lipid Solubility of the Drug

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

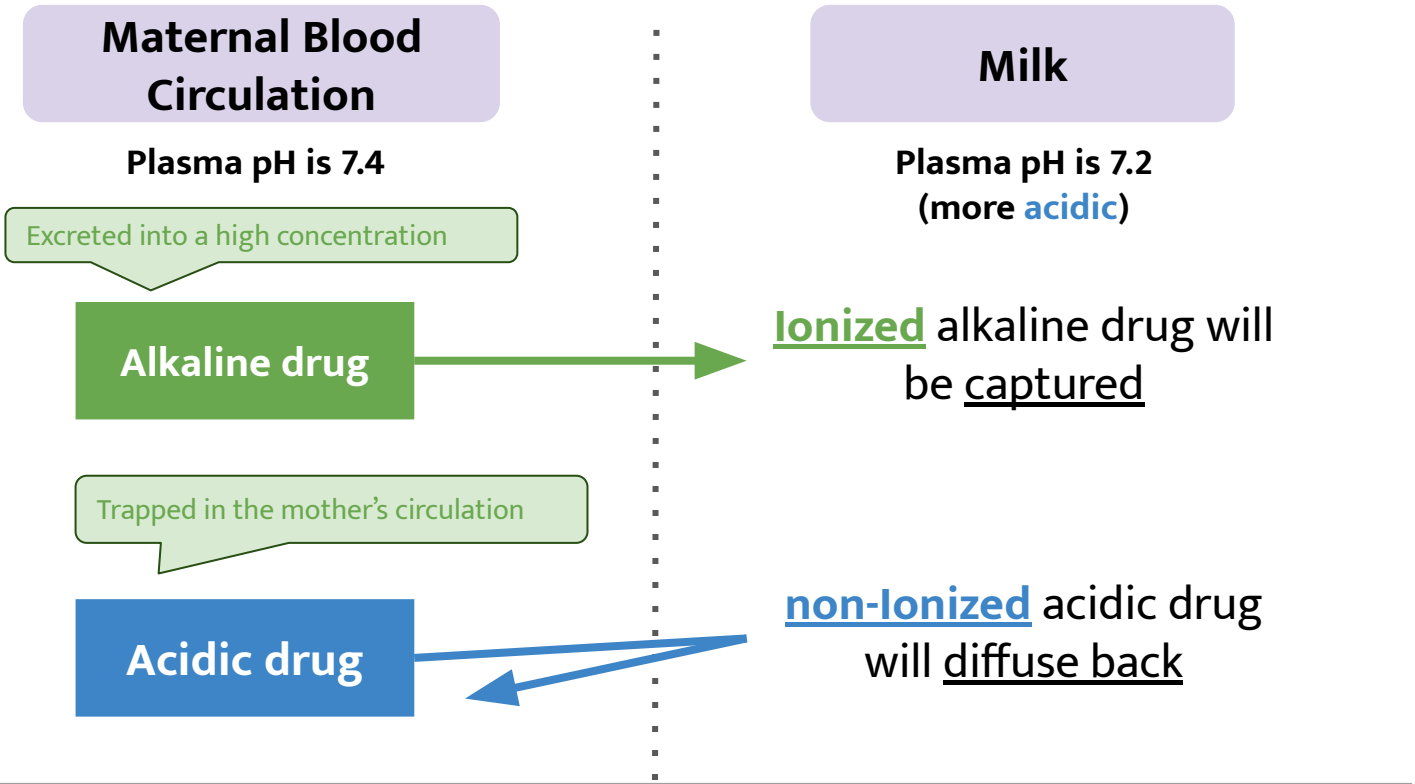
3. Degree of Ionization

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

4. pH of the Drug

- ❖ pH of milk is slightly more acidic than maternal blood.
- X **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**.

Remember the renal block? Imagine milk same as urine



لما يلاقي الدواء نفس وسطه راح يصير له اعادة امتصاص (في حالتنا اذا كان الدواء حمضي والوسط اللي رايح له حمضي كذلك (الحليب) فراح يصير للدواء اعادة امتصاص، لكن اذا الدواء قاعدي والوسط اللي رايح له حمضي، هنا بيتلاقى المتضادان وبيحصل بينهم مضاربة وهم متشابكين مع بعض لما يطلعون من الجسم

From team 435

5. Plasma Protein Binding

- ❖ 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**

Important note: warfarin can cross placental blood barrier but CANNOT cross to breast milk, so it's not safe during pregnancy but can be used during breastfeeding

6. Half Life

Drugs will be excreted before feeding

- Avoid the use of drugs with **long** half lives.
- **short** half life (t ½) are preferable.
- Oxazepam vs diazepam (oxazepam has short duration of action so, it has less exposure to the baby, while diazepam has long duration of action. So oxazepam good, diazepam not good:))

7. Volume of Distribution

In pregnancy imagine the fetus as another organ so if we have high Vd it will definitely go to it, so low Vd is preferable in pregnancy, but in case of breastfeeding if it's low it means it's concentrated in blood thus transports to milk and that is why high Vd is preferable in pregnancy

- Transfer of drugs from maternal blood to milk is low with drugs that have **large volume** of distribution (Vd).

لأن الام لما تاخذ دواء له فوليوم دستربيوشن عالي فالدواء راح يتوزع في كل الانسجة ويقل التركيز بالدم ومايصير في الحليب الا كمية قليلة. لكن لو كان قليل ماراح يتوزع في الانسجة ويتركز بالدم فيوصل الحليب اكمية اكبر.

Factors Related to Neonates

- Age & Health status
- Body weight

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

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

Special precautions are required in:

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

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).

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 (oral).

Maternal drug concentration

Dose of the drug

It means if we can reduce the dose and still get therapeutic effect in mother we should lower the dose

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.

Mindmap credits for team 435

Oxidizing drugs

Examples: **antibiotics** (sulfonamides, trimethoprim), **antimalarials** (primaquine)

Neonatal Hyperbilirubinemia

Premature infants or infants with inherited G6PD deficiency are susceptible to oxidizing drugs that can cause hemolysis of RBCS → ↑bilirubin (hyperbilirubinemia) → ↑Kernicterus.

Neonatal Methemoglobinemia

Infants under 6 months of age are particularly prone to develop methemoglobinemia upon exposure to some oxidizing drugs.

RECALL, **Methemoglobin** is an oxidized form of hemoglobin that has a decreased affinity for oxygen → tissue hypoxia

Drugs & Lactation

1. Drugs contraindicated during lactation

Only few drugs are totally contraindicated

Drug	Contraindication
Anticancer drugs (doxorubicin, cyclophosphamide, methotrexate)	❖ Cytotoxicity & neutropenia ❖ Cyclophosphamide is C.I in pregnancy too
Radiopharmaceuticals (radioactive iodine)	-

CNS acting drugs (amphetamine, heroin, cocaine)	-
Immunosuppressants (cyclosporine)	-
Alcohol & Lithium	❖ They have high milk to plasma rate. ❖ Low molecular weight.
Chloramphenicol	❖ Bone marrow suppression
Atenolol	❖ Beta-blocker, C.I because of its conc. Is high in milk
Potassium iodide	❖ Thyroid effect
Ergotamine Used for migraine headache	❖ Vomiting ❖ Diarrhea ❖ Convulsions in infants
Tobacco smoke	❖ Vomiting ❖ Diarrhea ❖ restlessness for the baby ❖ decreased milk production ❖ increase respiratory and ear infections.

Drugs & Lactation

Dopamine and prolactin have inverse relationship

2. Drugs that can suppress Lactation

These drugs reduce prolactin. (without harmful effect, it just reduce the volume of milk)

Drug	info.
Levodopa	❖ dopamine precursor
Bromocriptine	❖ dopamine agonist
Estrogen	❖ Or oral contraceptives that contain high-dose of estrogen and a progestin.
Androgens	-
Thiazide diuretics	Different from the others, doesn't work centrally on prolactin

Drugs & Lactation

Still no harm to the baby

3. Drugs that can augment lactation

Dopamine antagonists : they stimulate prolactin secretion → galactorrhea

Drug	info.
Metoclopramide	❖ antiemetic
Domperidone	❖ antiemetic
Haloperidol	❖ antipsychotic
Methyldopa	❖ antihypertensive
Theophylline	❖ used in asthma

Antibiotics

Back to harmful drugs

Note: drugs mentioned are same as pregnancy, what is okay for pregnant is okay for breastfeeding

Drug	info.
Penicillins (Ampicillin, amoxicillin)	✓ No significant adverse effect ❖ allergic reactions, diarrhea
Cephalosporins	✓ No significant adverse effect ❖ Alterations to infant bowel flora
Macrolides (erythromycin, clarithromycin)	
Quinolones	❖ Theoretical risk of arthropathies X Should be avoided
Chloramphenicol	❖ "Gray baby" syndrome X Should be avoided
Tetracyclines	❖ Absorption by the baby is probably prevented by chelation with milk calcium. X Avoid due to possible risk of teeth discoloration.

Sulfonamides (co-trimoxazole)	❖ hyperbilirubinemia ⟶ neonatal jaundice X Should be avoided in premature infants or infants with G6PD deficiency
Sedatives/Hypnotics	
Barbiturates (phenobarbitone)	X Lethargy, sedation, poor suck reflexes with prolonged use.
Benzodiazepines, Diazepam, Lorazepam	✓ **Single use** of low doses is probably safe. X Lethargy, sedation in infants with **prolonged use**.
Antidiabetics	
Insulin	✓ Safe
Oral antidiabetics	✓ compatible Remember it's contraindicated in pregnancy
Metformin	X avoid due to **lactic acidosis**
Analgesics	
Paracetamol	✓ Safe
Ibuprofen	✓ compatible
Aspirin	X avoid due to theoretical risk of **Reye's syndrome**
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.

Anti-convulsants (antiepileptics)

Carbamazepine	✓ Preferable over others ❖ **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	X **AVOID**

Not in pregnancy

Antihistamines

Sedating antihistamines (Diphenhydramine)	X **AVOID**
Non-sedating antihistamines (Loratadine)	✓ low levels of transfer into breast milk and these would be considered the preferred choice antihistamines for a breastfeeding mother.

Others

Oral contraceptives	✓ Non hormonal method should be used. X Avoid estrogens containing pills ○ **Estrogens → ↓ milk quantity** ✓ Progestin only pills or mini pills are preferred for birth control.
Antidepressants: SSRI	✓ **Paroxetine** is the preferred SSRI in breastfeeding women.
Antiasthmatics	✓ **Inhaled corticosteroids - prednisone**

Imp bc postpartum depression is common

Summary for choice of drug

- ❖ Drugs known to have serious toxic effects in adults are **avoided**
- ✓ **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** drugs in infants

General Considerations

1. Infants should be monitored for adverse effects e.g. feeding, sedation, irritability, rash, etc.
2. Drugs with no safety data should be avoided or lactation should be discontinued
3. Do not guess
4. Use the following sources:
   a. Use Medication and Mothers' Milk (www.iBreastfeeding.com)
   b. Use lactmed or toxnet (http://toxnet.nlm.nih.gov)

Quiz

Q1: which one of the following characteristics would you look for when prescribing a drug to a lactating mother?

A. Low molecular weight
B. Lipid soluble
C. High degree of ionization
D. Long half life.

Q2: all of the following drugs can augment lactation except:

A. Metoclopramide
B. Levodopa
C. Domperidone
D. Theophylline

Q3: sulfonamides should be avoided by a lactating mother in case of :

A. Prematurity
B. Low birth weight
C. Infants with G6PD deficiency
D. Infants with respiratory distress

Q4: a woman has postpartum depression ,which antidepressant is preferred if she's breastfeeding

A. Paroxetine
B. Amitriptyline
C. Sertraline
D. Imipramine

Q5: which of the following drugs will suppress lactation :

A. Bromocriptine
B. Metoclopramide
C. Domperidone
D. Haloperidol

Q6: a baby known to have G6PD deficiency develops jaundice while breastfeeding. What drug most likely was taken by the mother?

A. Penicillin
B. Erythromycin
C. Primaquine
D. Tetracycline

Answers:
1) C
2) B
3) C
4) A
5) A
6) C

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Thanks for those who worked on the lectures :

Munira alhadlaq

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References:

✓ Doctors' slides and notes

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