Pharmacology 439

MED439

pharmacology Team 438

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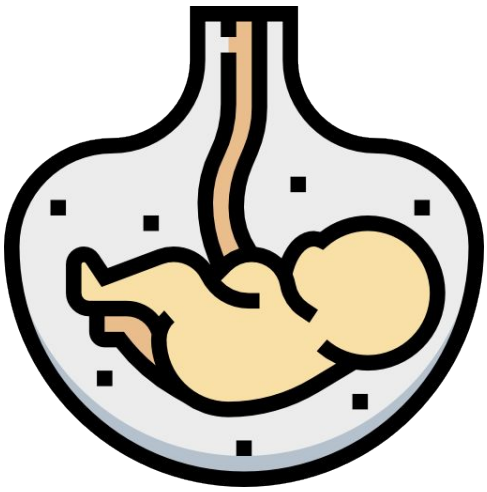


Reproduction Block

Pharmacology team 439

Drugs Affecting Breast milk & Lactation

Objectives:

By the end of the lecture , you should know:

- 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

Color index:

Black : Main content
Red : Important
Blue: Males' slides only
Pink : Females' slides only
Grey: Extra info or explanation
Yellow: Dr. notes (439)
Green: Dr. notes (438)

Breast Feeding

- 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%) (thus milk transfer is less than placental transfer)
    - However, even small amount 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

There are many pharmacokinetic and pharmacodynamics changes in pediatrics:

- Higher gastric pH[3]
- Lower rate of metabolism due to immaturity of liver enzymes
- Premature babies have very limited capacity for metabolism and excretion
- Higher concentration of free drug[1]
- Higher percentage of body water[2]
- Renal clearance is less efficient (↓ renal blood flow, ↓ Glomerular filtration rate)

Physiological Differences between Neonates and Adults of Pharmacokinetic Importance:

Prof. Hanan: numbers are not imp	Neonates	Adults
Gastric acid output (mEq/10kg/hr)	↓ 0.15	2
Gastric emptying time (min)	↑ 87	65
Total body water (% of body weight)	↑ 78 Hydrophilic drugs are more concentrated	60
Adipose tissue (% of b.wt.)	↓ 12	12-25
Serum albumin (gm/dL)	↓ 3.7 More free drug → more toxicity	4.5
Glomerular filtration rate (ml/min/m2)	↓ 11 Less clearance → more toxicity	70

Factors Controlling Passage of Drugs into Breast Milk

- Factors related to the **Drug**
- Factors related to the **Mother**
- Factors related to the **Neonate**

1: due to low protein binding.
2: affects the concentration of water soluble drugs.
3: infants produce less gastric acid

Factors Related to the Drug

Molecular Weight

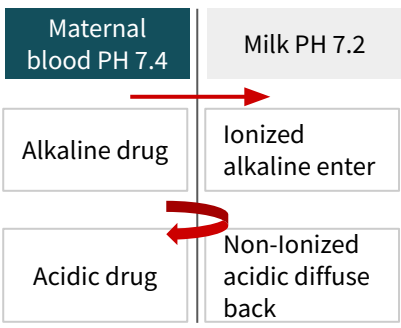
- Very small molecules (<200 Daltons) such as alcohol, equilibrate rapidly between plasma and breast milk via the aqueous channel surrounding alveoli
- **Large molecules drugs** (>800 Daltons) are **less likely to be transferred** to breast milk than low molecular weight
  - Insulin: MW > 6,000 Daltons
  - Heparin: MW 40,000 Daltons
- Monoclonal antibodies, pass very poorly into milk after the 1st week postpartum, however they pass effectively during the first week
- 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

Lipid Solubility

- **Lipid soluble drugs pass more freely** into the breast milk than water soluble drugs. Think of milk as a lipid solution

Drug PH

- **pH of milk is slightly more acidic** (PH=7.2) than maternal blood (PH=7.4)
- 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



Prof. Hanan: If both drugs were lipid soluble and passed into breast milk, alkaline drugs become ionized in acidic medium (b.milk) which makes it difficult to diffuse back to plasma, thus remain in milk. While acidic drugs are non-ionized in acidic medium so they diffuse back to plasma

Degree of Ionization

- **Ionized form of drugs are less likely** to be transferred into breast milk[1]
  - E.g. **heparins** pass poorly into breast milk

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**[2]
  - Drugs with **high** protein binding capacity are preferable in lactation

Half Life

- Avoid the use of drugs with long half lives[3]
- ★ **Short half life are preferable**
- **Oxazepam** (short t1/2) vs **diazepam** (long t1/2)

Volume of distribution of drugs

- Transfer of drugs from maternal blood to milk is low with drugs that have **large volume of distribution (Vd)**
  - Large Vd ⟶ less conc. Of drug in the blood, more in the tissue (↓risk)
  - Small Vd ⟶ drug concentrates in plasma and excreted in milk

1: i.e. polar drugs are less likely to be transferred to breast milk.
2: remember that warfarin is totally contraindicated in pregnancy, but here we see that it can be given to breastfeeding women.
3: ↑ time in circulation ⟶ ↑ risk of transport to milk (esp CNS drugs as they are lipid soluble)

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Factors Related to the Mother

Route of Admin.

- 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

Time of Breast feeding

- The **concentration** of the drug in the milk at the time of feeding

★ Lactating mother should take medication **just after nursing**[1] **and 3- 4 hours before**[2] **the next feeding** ; to allow time for drug to be cleared from the mother's blood so drug concentration in milk will be low.

Health Status

- **Breastfeeding is contraindicated in case of:**
  - HIV- positive women
  - Active, untreated TB in mother
  - Herpes on breast
  - Use of illegal drugs[3] by mother
  - Certain medications used on a chronic basis

Dose of The Drug

Maternal Drug Conc.

Factors Related to the Neonate

Age | **Body Weight** | **Health Status**

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 (e.g oral medications)
- The **ability** of the baby to eliminate the drug (depends on age)

We treat milk here like it's a drug so we look at the dose, absorption and clearance.

Age & Health Status **Skip it**

Newborn

(less than one month)

1. **Preterm neonates:** born before 38 weeks of pregnancy
2. **Full-term neonates:** 38-42 weeks of gestational age

Infants (babies)

(1 month -12 months)

Children

(1 -12 years)

1. **Toddler (young child):** 1-5 years
2. **Older child:** 6-12 years

Adolescent

(13-18 years)

1: very beneficial especially in drugs with short duration of action as their action will have already been diminished by the next nursing time.
2: most drugs' half-life peak value is within 2 hrs, 3-4 hrs gap ensures low concentration of the drug in mother's plasma → minimal risk of transfer.
3: e.g. cocaine, heroine, and marijuana.

Age & Health Status Cont...

Special cautions are required in:

1. Premature infants
2. Low birth weight
3. **Infants with G6PD deficiency**
4. Infants with impaired ability to metabolize\excrete drugs. **E.g Hyperbilirubinemia**

Neonatal Methemoglobinemia

Methemoglobin: is an oxidized form of hemoglobin that has a decreased affinity for oxygen → tissue hypoxia.

Infants under 6 months of age are particularly prone to develop methemoglobinemia **upon exposure to some oxidizing drugs**[1]

Infants < 6 months if given an oxidant:

- Normal infant will develop metHb
- **G6PD-deficiency** infant will develop metHb and hyperbilirubinemia

Neonatal Hyperbilirubinemia

When does it occur? Premature infants or infants with inherited **G6PD deficiency are susceptible to oxidizing drugs** that can cause hemolysis of RBCs→↑ bilirubin (hyperbilirubinemia) →↑ Kernicterus

E.g of oxidizing drugs:

1. **Antibiotics:** Sulfonamides[2], Trimethoprim
2. **Antimalaria:** Primaquine

Drugs During Lactation

Drugs are C.I during lactation

Only few drugs are totally contraindicated:

1. **Anticancer drugs** e.g. Doxorubicin, cyclophosphamide, methotrexate. They will cause cytotoxicity and neutropenia
2. **Radiopharmaceuticals** e.g. radioactive iodine
3. **CNS acting drugs** e.g amphetamine, heroin, cocaine
4. **Alcohol & Lithium** (they have high milk to plasma ratio)
5. **Chloramphenicol** (causes bone marrow suppression)
6. **Atenolol**
7. **Potassium iodide** (thyroid effect)
8. **Immunosuppressants** e.g. cyclosporine
9. **Ergotamin** (used for migraine headaches) cause vomiting, diarrhea, convulsion in infants
10. **Tobacco smoke:** nicotine can cause vomiting, diarrhea and restless for the baby, decreased milk production & increase respiratory and ear infection

Drugs can suppress lactation

These drugs reduced prolactin:

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

Drugs can augment lactation

Dopamine antagonists: they stimulate prolactin secretion galactorrhea

1. **Metoclopramide & Domperidone** (antiemetic)
2. **Haloperidol** (antipsychotic)
3. **Methyldopa** (antihypertensive drug)
4. **Theophylline** (used in asthma)

1: oxidizes hemoglobin to methemoglobin

2: (combining our knowledge from lecture 1) so now we know of two ways that sulfonamides can cause hyperbilirubinemia by displacing bilirubin from albumin, and by being an oxidizing agent (in G6PD) and by protein displacement of bilirubin (affecting fetus during pregnancy).

Drugs During Lactation Cont...

Drugs can be used	Drugs should be avoided
Antibiotics[1]	
Penicillins e.g Ampicillin[2], Amoxicillin (No significant ADRs but mostly allergic reactions and diarrhea)	**Quinolones** (Theoretical risk of arthropathies)
	Chloramphenicol (Avoid) (Gray baby syndrome)
Cephalosporins **&** **Macrolides** e.g Erythromycin, clarithromycin (No significant ADRs, alternation to infant bowel flora)	**Tetracycline** (Absorption by the baby is probably prevented by chelation with milk calcium, avoid due to possible risk of teeth discoloration)
	Sulfonamides (co-trimoxazole) (Cause hyperbilirubinemia-neonatal jaundice, **Should be avoided in premature infants or infants with G6PD deficiency**)
Drugs of choice among Antibiotics: Cephalosporins and Penicillins	
Sedative / Hypnotics	
-	**Barbiturates** e.g phenobarbitone (Lethargy, sedation, poor suck reflexes with prolonged use)
Benzodiazepines e.g Diazepam, Lorazepam (**Single use** of low doses is probably safe)	**Benzodiazepines** e.g Diazepam, Lorazepam (Lethargy, sedation in infants with prolonged use)
Antidiabetic	
Insulin (safe)	**Metformin** (avoid due to lactic acidosis[3])
Oral antidiabetics (compatible/used)	
Drugs of choice among Antidiabetics: Insulin and Oral antidiabetic	
Analgesics	
Paracetamol (safe)	**Aspirin** (Theoretical risk of Reye's syndrome)
Ibuprofen (compatible)	
Drugs of choice among Analgesic: Paracetamol (Acetaminophen)	
Antidepressants	
Selective Serotonin Reuptake Inhibitors (SSRI) e.g Paroxetine is the preferred SSRI	-

1: basically beta lactams and macrolides are allowed.
2: increase infant's bowel movements → diarrhea (but still a safe choice)
3: even though it is a very rare side effect of metformin, one should never risk it.

Drugs During Lactation Cont...

Drugs can be used	Drugs should be avoided
Antithyroid	
Propylthiouracil (Highly protein bound so less likely to be excreted)	**Carbimazole, Methimazole, Potassium iodide** (May suppress thyroid function in infants)
	Radioactive iodine (Permanent hypothyroidism in infant, breastfeeding is C.I)
Drugs of choice among Antithyroid: Propylthiouracil is preferred over others and should be used rather than Carbimazole or Methimazole	
Anticoagulants	
Heparin (better) (Safe & not present in breast milk)	-
Warfarin[1] (can be used & very small quantities found in breast milk → **monitor the infant's prothrombin time during treatment**)	
Drugs of choice among Anticoagulants: Both Warfarin and Heparin	
Anticonvulsants	
Carbamazepine[3] (Prefered over others, compatible with breastfeeding)	**Lamotrigine** (avoid)[2]
Phenytoin (amount entering breast milk are not sufficient to produce ADRs)	**Valproic acid** (Infants must be monitored for CNS depression, better to be avoided in the first place)
Drugs of choice among Anticonvulsant: Carbamazepine and Phenytoin	
Oral Contraceptive (non-hormonal methods should be used)	
Progestin only pills or mini-pills (Preferred for birth control)	**Estrogens** containing pills (Estrogen decreases milk quantity)
Drugs of choice among Oral contraceptive: Progestin only pills or mini-pills	
Antihistaminics	
Non-sedating antihistamine e.g Loratidine	**Sedating** antihistamine e.g Diphenhydramine
Antiasthmatic	
Inhaled corticosteroid e.g prednisone	-

1: safe in lactation unlike pregnancy(teratogenic)
1: drug of choice.
2: lamotrigine is the first choice to treat pregnant women with epilepsy

★ Drug of choice in lactation

We'll ask you about a specific disease in the table and you should answer with the best medication

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 Choices of Drugs

- 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 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. Don't guess, do not predict, only use when you know for sure it is safe.

Quiz

MCQ

Q1- Strategies to lower infant exposure to medications through breast milk include all of the following except:

A- Recommend a drug with a shorter half-life
B- Recommend a drug with a poor oral bioavailability
C- Recommend a highly protein bound drug
D- Recommend a highly lipophilic drug

Q2- Breastfeeding is contraindicated in all of these conditions except:

A- Mother using illegal drugs B- Diabetic women
C- HIV-positive women D- women with Active TB

Q3- Breastfeeding mother was taking a drug, she noticed a decrease in milk quantities, what's the most likely drug she was taking?

A- Estrogens B- Metformin C- Potassium Iodide D- Lamotrigine

Q4- Which of the following drugs is concentrated in breast milk and should be avoided by women who are breastfeeding?

A- Heparin B- Penicillin C- Alcohol D- cephalosporins

SAQ

- A 24-years-old female has postpartum depression after delivery.

Q1-Which antidepressant drug is preferred if she's breastfeeding?
Q2-What is the M.O.A of that drug?

- A 30-years-old breastfeeding female came to the clinic with symptoms of infection.

Q3-Name 2 types of antibiotics that can be used safely in this case.
Q4-If her baby known to have G6PD deficiency and he develops jaundice while breastfeeding. Which antibiotic drug most likely was taken by the mother?

- A 29-years-old diabetic female had a baby and she would like to breastfeed her baby

Q5-Which antidiabetic should be avoid in this case? Why?

Answers:

MCQ

Q1	D
Q2	B
Q3	A
Q4	C

SAQ

Q1	Paroxetine
Q2	Selective serotonin reuptake inhibitor (SSRI)
Q3	Penicillins - Cephalosporins
Q4	Sulfonamides
Q5	Metformin due to lactic acidosis

Thank you for all the love and support you gave the team in those two years!

Hope we made the context much easier to study.
God bless you, Future doctors.

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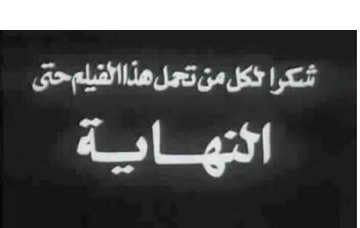

Any last words?

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