Reproductive System

PHARMACOLOGY 432 TEAM

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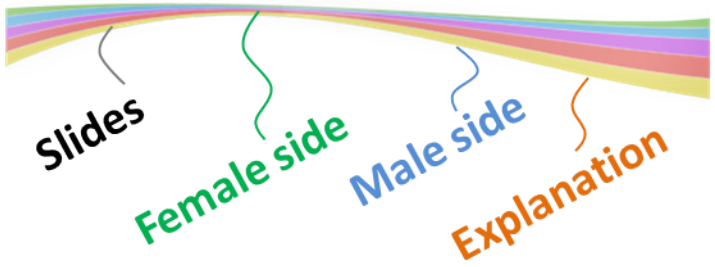


LECTURE'S TITLE

Learning Objectives:

1. Relation of drugs and lactation
2. Factors modifying passage of drugs in milk
3. Effects of drugs on milk production
4. Role of lactation on drugs excretion
5. Drug safety during lactation / use of safe drugs
6. Drugs contraindicated during 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 & 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. (all the execratory mechanisms are going down in babies)

Pediatric population are classified into:

- **Newborn:** less than one month old
  - Preterm neonates: born before 38 weeks of pregnancy (it's the harmful stage)
  - 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 in pediatric:

- Higher gastric PH
- Higher concentration of free drug
- Higher percenrage of body water
- Neonate's especially premature babies have limited capacity for metabolism and excretion.
- Neonates have very limited rate of metabolism due to immaturity of liver enzymes.
- Renal clearance is less efficient: (decrease Renal blood flow – decrease GFR).
- 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.

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 that affect passage of drugs into breast milk:

Factors related to drugs

Molecular weight:

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.

Volume of distribution Transfer of drug from maternal blood to milk is low with drugs that have large volume of distribution (Vd)to prevent from staying from blood.let it stay in tissues.

Half life of drug

Avoid the use of drugs with long half lives

short half life (t ½) are preferable.

Lipid solubility of the drug:

Lipid soluble drugs pass more freely into the breast milk than water soluble drugs.can easily cross any membrane

Degree of ionization:

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

Plasma protein binding of drugs

Drugs circulate in maternal circulation in unbound (free) or bound forms to albumin.

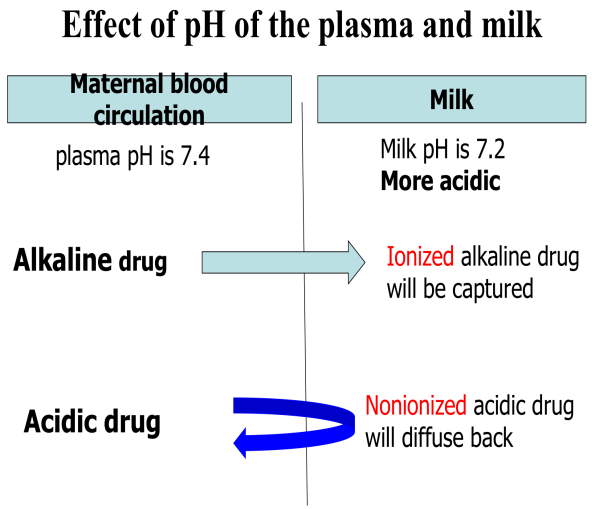
Only unbound form gets into maternal milk.

Definition of good protein binding > 90%

e.g. warfarin also heparin could be prescribed

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.maternal circulation



Factors that affect passage of drugs into breast milk:

Factors related to mother

Route of administration (to minimize exposure of drug)

- 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 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.(injection-minutes)

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

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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 that affect passage of drugs into breast milk:

Factors related to neonates

Age -Body weight(premature lower body weight than mature)- 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(even those with full term-gestation) - Infants with G6PD deficiency- Infants with impaired ability to metabolize /excrete drugs e.g. hyperbilirubinemia.(physiological jaundice)

Pathological conditions

Neonatal hyperbilirubinemia

Premature infants or **infants with inherited G6PD(found in RBC's membrance(antioxidant)** deficiency are susceptible to oxidizing drugs that can cause → hemolysis of RBCS →↑ bilirubin (hyperbilirubinemia) →↑ Kernicterus(go BBB)

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.**

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Drugs contraindicated during lactation:

Anticancer drugs	CNS acting drugs	Lithium (anti manic Drug)	Atenolol	Radioaph armaceu ticals	Potassium iodide
Risk of Growth retardation Doxorubicin, cyclophosphamid e, methotrexate	Amphetamine, heroin, cocaine , BZDs , Bulbutarates & even Smoking	high concentration of the drug will pass with the milk and appear as skin rash on the baby	Risk of Bradycradia and Hypoglycemia	Radioactive iodine	risk of Hypothyroidism **Chloramphenic ol antibiotic Remember gray baby syndrome**

Drugs that can suppress lactation: (does not produce harmful actions) >> reduce prolactin

Levodopa	Bromocriptin e	Androgens	Estrogen,combi ned oral contraceptives	Thiazide diuretics	Ergot derivatives
(dopamine precursor). Dopamine will Inhibit Prolactin leading to Milk Suppression	(dopamine agonists). Same Action as Dopamine		that contain high-dose of estrogen and a progestin.take mini pills or progestrins only		anti Migraine Drugs

Also, Pyridoxine, and MAO inhibitors suppress lactation

Drugs to be avoided during lactation:

Barbiturates: Phenobarbitone	Benzodiazepines: diazepam	Antithyroid drugs: carbamizole	Hormonal contraceptives: estrogen only	Analgesics : Aspirin	Antibiotics: Tetracyclines

Note:
These drugs are contraindicated also but they can be used under some restrictions when there's no other choice

Dopamine antagonists: they stimulate prolactin secretion (Hyper-Prolactinemia) such as: like anti-physicotics,have risk parkinsonism

Drugs that can augment lactation:

Metoclopramide (antiemetic)	Haloperidol (antipsychotic)	Phenothiazine	Methyl dopa (antihypertensive drug) *preferred in pregnancy also	Theophylline (used in asthma) Has narrow theraputic index	Domperidone (antiemetic)

Note:

- Infant with **G6PD deficiency** may develop **hemolysis** and **hyperbilirubinemia** with **sulphonamides** and antimalarial drug **primaquine**
- **Some antibiotics are contraindicated in lactating women e.g. chloramphenicol**

Antibiotics

Penicillins Ampicillin amoxacillin	No significant adverse effect allergic reactions, diarrhea (!st prescribed)
Cephalosporins	If she's allergic to penicllins or the baby has diarreah
Macrolides erythromycin clarithromycin	No significant adverse effect Alterations to infant bowel flora
Sulfonamides (co-trimoxazole)	hyperbilirubinemia -neonatal jaundice Should be avoided in premature infants or infants with G6PD deficiency
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.theoritically not proven
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.(addiction to mom&baby)
Benzodiazepines Diazepam Lorazepam	Single use of low doses is probably safe. Lethargy, sedation in infants with prolonged use.

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.

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

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 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

General considerations to minimize risk to nursing infant:

- The safest drug should be chosen.
- Route of administration (topical, local, inhalation) instead of an oral form.
- Poorest oral bioavailability
  - o Inhaler Restricted to the Respiratory system
  - o Topical Restricted to the Skin
- Lowest lipid solubility.
- Shortest half-life
- Highest protein-binding ability.
- Lactating mother should take medication just after nursing and 3-4 hours before the next feeding.
- 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.

Cautions required in:

1. Premature infants
2. Low birth weight

} **at high risk of developing side effects**

3. Infants with impaired ability to metabolize/excrete drugs eg. sick babies
4. Infants with G6PD deficiency

Summary

To minimize the ADRs of the drugs in lactation we use a drug having these characters :

- non lipid soluble (water soluble) → ionized
- High molecular weight
- acidic drug
- Summary:
- Short half life
- high volume of distribution

Drugs of choice in lactation:

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

1. **Which one of the following drugs should be avoided during lactation :**
   A. Chloramphenicol
   B. Insulin
   C. Erythromycin
   D. Penicillin

2. **Which one of the following drugs can be given during lactation :**

A. Quinolones
B. Sulphonamides
C. L-dopa
D. Heparin

Answers: 1-A, 2-D

3- Which one of the following drugs increases the risk of growth retardation:

A. Amphetamine
B. Doxorubicin
C. Atenolol
D. Potassium Iodide

4- Which one of the following drugs Appear as skin rash on the baby :

A. Lithium
B. Cocaine
C. L-dopa
D. Penicillin

Answers: 3-B, 4-A

5- A newborn baby with G6PD deficiency presented with hemolysis and yellowish appearance. Which of the following drugs the mother are taking that could cause his symptoms:

A. Chloramphenicol
B. Erythromycin
C. Primaquine
D. Propylthiouracil

6- Which one of the following drugs is safe in a lactating mother that don't want to have another child :

A. Combined oral contraceptive
B. Minipills
C. L-dopa
D. Atenolol

Answers: 5-C, 6-B

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