PT431 Team Pharmacology

Reproductive Block

Lecture 5
Drugs affecting breast milk and lactation

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LACATION

- ***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.

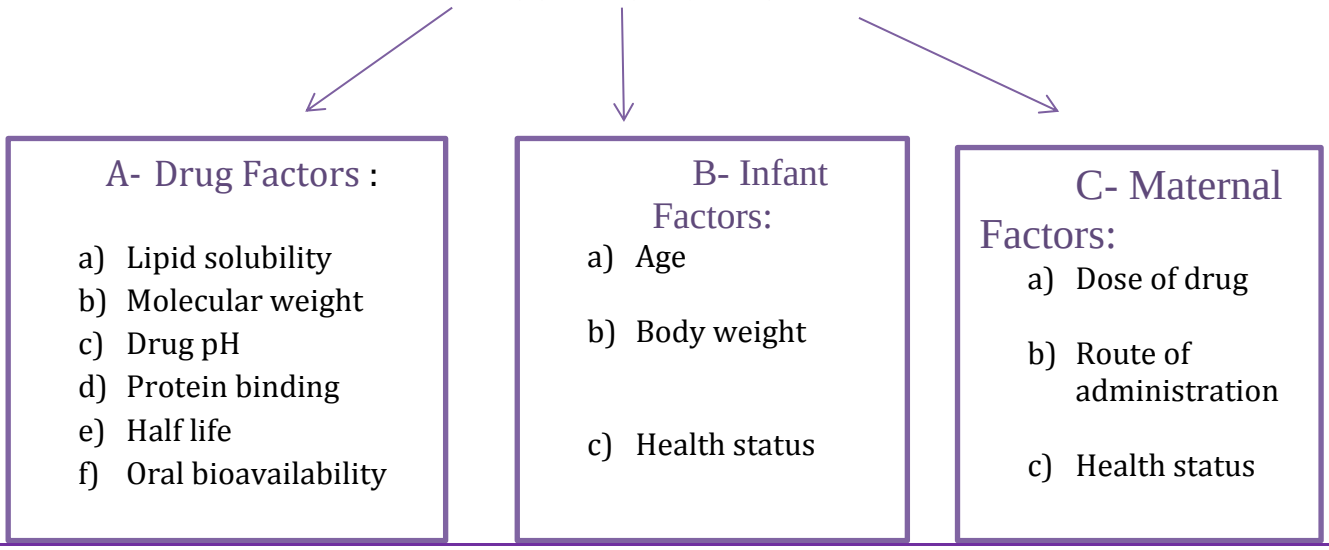
Pediatric populations are classified into:

New-born	**Less than 1 month**
- **Preterm neonate**	Born before 38 week of pregnancy
- **Full-term neonate**	38-42 weeks of gestational age
Infant (Babies)	1 month – 12 months
Children	1-2 years
Toddler (young child)	1-5 years
Old child	6-12 years
Adolescent	13-18 years

Pharmacokinetics in paediatrics:

- ✓ 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: (↓Renal blood flow - ↓ 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.

Factors controlling passage of drugs into breast milk:



Factors controlling passage of drugs into breast milk

1. Drugs factors

Lipid solubility: lipid soluble drugs pass more freely into the breast milk (↑Effect on the baby)

Molecular weight: low molecular weight drugs are more likely to be transferred to breast milk than high molecular weight (↑Moclecular weight drugs are recommended because they don't pass with the milk)

E.g. Insulin: MW > 6,000 Daltons (doesn't pass with the milk Because of ↑ Molecular weight)

Heparin: MW 40,000 Daltons

Ethanol: MW 200 (concentration of Ethanol in the baby's blood appears equal to the Mother's blood due to ↓ Molecular weight)

Degree of ionization: Nonionized forms of drugs are more likely to be transferred into breast milk (linked with water solubility).

pH of drug:

- Weakly alkaline drugs tend to be concentrated in milk.
- Weakly acidic drugs don't enter the milk to a significant extent and tend to be concentrated in plasma (does not produce a harmful effect on the baby) (e.g. Penicillin)

Plasma protein binding of drugs

- Medications circulate in maternal circulation bound or unbound (free) to albumin
- Only **unbound** drug gets into maternal milk (able to cross any tissue membrane)
- Definition of good protein binding = > 90% (e.g. Warfarin is 99% bound to plasma protein so it does not appear in the milk)

2. Mother factors

- **Route of administration (oral administration is NOT recommended)**
- **Maternal drug concentration (drug concentration at time of feeding)**

Transfer of drug from mother's blood to milk is low with drugs that have:

Large volume of distribution (Vd): (because concentration of the drug will be↑ In the tissue rather than the blood)

Short half-life (t ½): (drug will be excreted in a short time before so it won't harm the baby)

3. Infant's factors

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

- ✓ The concentration of the drug in the milk at the time of feeding.
- ✓ The amount of milk consumed.
- ✓ The amount of drug absorbed.
- ✓ The ability of the baby to eliminate the drug

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
    - Inhaler →Restricted to the Respiratory system
    - 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**

Neonatal Hyperbilirubinemia

Premature infants or infants with inherited glucose -6- phosphate dehydrogenase (G6PD) deficiency are susceptible to **oxidizing drugs** that can cause ↑ **Haemolysis** of RBCS & ↑ **Bilirubin** (hyperbilirubinemia)

Therefore Causing **Kernicterus** (irreversible Brian Damage).

G6P → Anti-Oxidant Enzyme located on the RBC

Deficiency of G6P → ↑ Vulnerability to any Oxidizing agent causing Destruction to the RBC and Accumulation of Bilirubin

The baby's liver is not able to get rid of bilirubin in large quantities

Examples for oxidizing drugs:

Antibiotics: (sulfonamides, trimethoprim, dapsone)

Antimalarial Drugs: (Primaquine)

Neonatal Methemoglobinemia

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

(Abnormal Haemoglobin Bind with Fe^{+3} (Ferric) "which is not able to bind with Oxygen" instead of Fe^{+2} (ferrous))

Infants under 6 months of age are particularly susceptible to methemoglobinemia upon exposure to some **oxidizing drugs** as:

Antibiotics (sulphonamides, trimethoprim, dapsone)

Topical anaesthetic (*benzocaine: applied to the gums in baby teething gels).

Drugs contraindicated during lactation:

- **Anticancer drugs (↑Risk of Growth retardation)**
    - **Doxorubicin, cyclophosphamide, methotrexate**
- **CNS acting drugs**
    - **Amphetamine, heroin, cocaine , *BZDs , Bulbutarates & even Smoking***
- **Lithium** (ant manic Drug) **:** (high concentration of the drug will pass with the milk and appear as skin rash on the baby)
- **Atenolol** (Beta-Blocker) → Risk of Bradycradia and Hypoglycemia
- **Radioactive iodine**
- **Potassium iodide** (risk of Hypothyroidism)

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

- **Levodopa** (dopamine precursor) → Dopamine will Inhibit Prolactin → Milk Suppression
- **Bromocriptine** (dopamine agonists)→ Same Action as Dopamine
- **Androgens**
- **Estrogen & combined oral contraceptives that contain high-dose of estrogen and a progestin.**
- **Thiazide diuretics**
- **Ergot derivatives** (anti Migraine Drugs)

Drugs that can augment lactation:

Dopamine antagonists: they stimulate prolactin secretion (Hyper-Prolactinemia) such as:

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

Anti-Biotics	
Penicillin **Ampicillin** **amoxicillin**	No significant adverse effect (compatible) allergic reactions, diarrhoea
Cephalosporins	No significant adverse effect (Compatible)
Chloramphenicol	"Gray baby" syndrome
Sulphonamides	**hyperbilirubinemia** -neonatal jaundice Should be avoided
Erythromycin	No significant adverse effect (Compatible)
Quinolones	AVOID Risk of arthropathies
Tetracyclines	Absorption by the baby is probably prevented by chelation (binding) with milk calcium. Risk of teeth discoloration.
Sedative/hypnotics	
Barbiturates (phenobarbitone)	Lethargy, sedation, poor suck reflexes Clinical monitoring is recommended
Benzodiazepines (diazepam)	Lethargy, sedation in infants Clinical monitoring is recommended
Anti-diabetics	
Insulin **Oral anti-diabetics** **Metformin**	safe compatible avoid due to lactic acidosis
Oral contraceptives	
Avoid estrogens containing pills **Estrogens ↓milk quantity** **Progestin only pills or minipill are preferred for birth control.**	
Antithyroid drugs	
Propylthiouracil **Carbimazole** **Methimazole** **potassium iodide** **Iodine (radioactive)**	May suppress thyroid function in infants. Propylthiouracil should be used rather than carbimazole or methimazole. Permanent hypothyroidism
Anticoagulants	
Heparin **Warfarin**	Heparin is not present in breast milk. Warfarin can be used
Anticonvulsants	
Carbamazepine **Phenytoin**	Are preferable over others Amounts entering breast milk are not sufficient to produce adverse effects
Cytotoxic drugs	Breast feeding should be avoided
Lithium	AVOID (Large amounts are detected in milk)
CVS drugs	
Atenolol	Risk of bradycardia and hypoglycaemia

Summary & MCQs

Summary:

1- Breastfeeding is very important for the immune system of the infant.
2- There are 3 types of Factors controlling passage of drugs into breast milk (Drug , mother & infants).
3- The age of the infants affect his liability to be harmed by the drugs.
4- We have to consider the pharmacokinetics of each drug and it possibility to pass to the breast milk (lipid solubility, molecular weight etc..).
5- Neonatal Hyperbilirubinemia is a condition which result from

   accumulation of bilirubin because of hemolysis caused by certain drugs.

6- As a doctor you should know which drugs considered safe and which considered unsafe in treating lactating women.

MCQs:

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

1- A
2- D