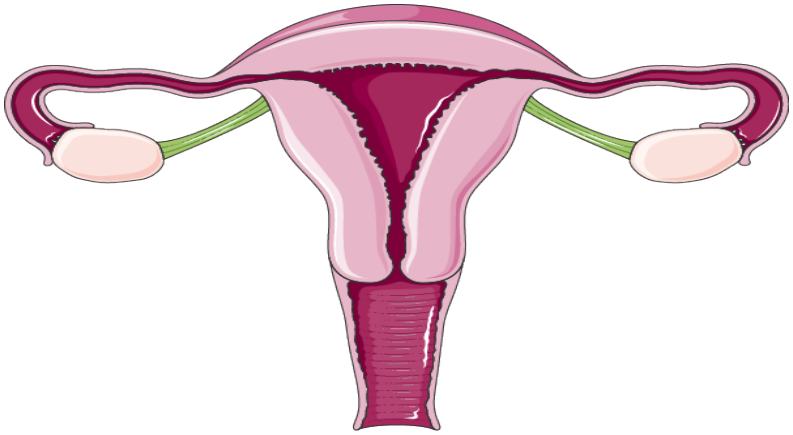
MEDICINE
KING SAUD UNIVERSITY

436 team
pharmacology



8: Drugs Affecting Breast Milk And 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 breast feeding
5. Know drugs that may enhance lactation.

Color index

- **Doctors' notes**
- **Drugs names**
- **Extra information and further explanation**
- **Important**
- **Mnemonics**

Kindly check the editing file before studying this document

Lactation

Breast feeding

- Breast feeding is very important because breast milk is the healthiest form of milk for babies. And it also build especial bond between the mother and the baby.
- 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 amount of some drugs may be of significance for the sulking child. معظم الادوية لا تستطيع ان تتركز بكميات كبيرة في الحليب لكن بعضها حتى الكميات القليلة يكون تأثيرها قوي
- Few drugs are absolutely contraindicated
- Some drugs may increase or decrease milk yield (female slides only)
- There are many pharmacokinetic and pharmacodynamics changes in pediatrics (only male slides)

Pharmacokinetics changes in pediatrics

- Higher gastric pH
- Higher concentration of free drug (protein binding in new born is ↓)
- Higher percentage of body water
- Lower rate of metabolism due to immaturity of liver enzymes
- Renal clearance is less efficient: (↓ renal blood flow, so ↓ Glomerular Filtration Rate)
- Premature babies have very limited capacity for metabolism and excretion (born before 37 weeks. Very sensitive more harmful effects)

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)	When the the body water increase → the fat decrease → the drug that is usually stored in fat will be free → free drug causes action	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

Factors Related to Drugs

Molecular weight

- Very small molecules (<200 Daltons) such as alcohol, equilibrate rapidly between plasma and breast milk via the aqueous channel surrounding alveoli = non-compatible
- Large molecules drugs (>800 Daltons) are less likely to be transferred to breast milk than low molecular weight = compatible
  - Insulin: MW > 6,000 Daltons
  - Heparin: MW 40,000 Daltons
- Monoclonal antibodies, pass very poorly into milk after the 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. اخطر مرحلة بعد أسبوع من الولادة لان تكون البيرمابيلتي عالية فأي دواء نعطيه ممكن يمر

Lipid solubility

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

Drug pH

Degree of ionization

- Ionized form of drugs are less likely to be transferred into breast milk
- E.g. heparins pass poorly into breast milk. highest degree of ionization → charged → water soluble (safer)

Protein binding

Half life

- Avoid the use of drugs with long half lives long duration of action → exist in her body for long time → increase exposure → high risk of ADRs
- Short half life (t½) are preferable
- Oxazepam (short t½) vs diazepam (long t½).

Oral bioavailability

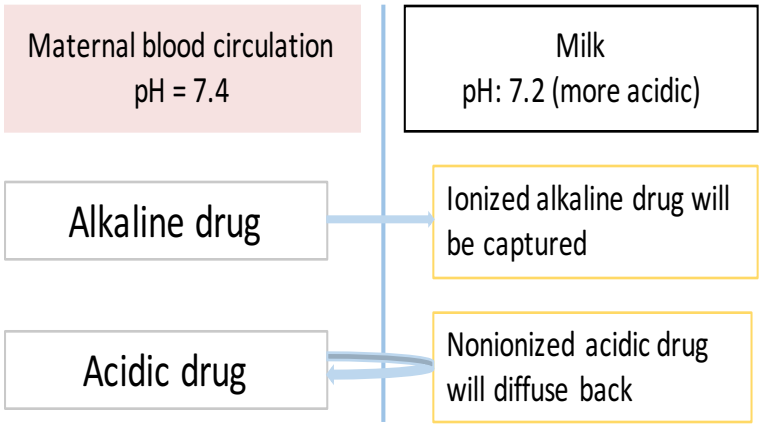
- Transfer of drugs from maternal blood to milk is low with drugs that have large volume of distribution (Vd). high Vd means it will be distributed in multiple body tissue → low concentration in blood → low concn. In milk.

Factors Controlling Passage of Drugs into Breast Milk

Factors Related to Drugs

- Molecular weight
- Lipid solubility
- Drug pH
- Degree of ionization
- Protein binding
- Half life
- Oral bioavailability

- pH of milk is slightly more acidic than maternal blood
- Week basic drugs tend to concentrate in breast milk and become trapped secondary to ionization
- Week acidic drugs don't enter the milk to a significant extent and tend to be concentrated in plasma



Weak acidic is better then weak basic during breast feeding, why? Bc week basic drug will enter the acid milk and get ionized (polar) so it can't go back again. Acidic drugs can't ionized in the acid milk (lipophilic) so it can cross the membrane and go back

- Drugs circulate in maternal circulation in unbound (free) or bound forms to albumin.
- Only unbound form gets into maternal milk. bc it will be trapped
- Definition of good protein binding > 90%
- e.g. warfarin

Factors Controlling Passage of Drugs into Breast Milk

Factors Related to Mother

Dose of the drug

The larger the dose → the more ability for the drug to be excreted in the milk and vice versa

Rote 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[1].

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 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')[2].

Health status

Breastfeeding is contraindicated in case of:

1- HIV-positive women

2- Active, untreated TB in mother

3- Herpes on breast

4- Use of illegal drugs by mother

5- Certain medications (used on a chronic basis 'female slides only').

Maternal drug concentration

[1] we should use the topical route and avoid the systemic route as much as possible

[2] Breast feeding is best done every 4h, oral drug need 2h to reach its peak , so the mother should take the drug before breastfeeding immediately, cause at the first breast feeding drug wont work and the next breastfeeding (after 4h from taking the drug) the maximum peak of drug will decrease → no affect of the drug on the baby

Factors Controlling Passage of Drugs into Breast Milk

Factors related to neonate

- Age
- Body weight
- 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.

Pediatric population (AGE & health status)

Newborn: less than one month old

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 of age

Children: 1-12 years of age

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

Adolescent: 13-18 years

Factors Controlling Passage of Drugs into Breast Milk

Age & health statue

- **Special caution are required in:**
  - ✓ Premature infants. has very little ability for metabolism and execration → longer duration of action → more harmful effect
  - ✓ Low birth weight
  - ✓ Infants with G6PD deficiency.
  - ✓ Infants with impaired ability to metabolize/excrete drugs, e.g. hyperbilirubinemia

Neonatal hyperbilirubinemia

- **When dose it occur?** Premature infants or infants with inherited G6PD deficiency are susceptible to oxidizing drugs that can cause hemolysis of RBCS → ↑ bilirubin (hyperbilirubinemia) → ↑ Kernicterus[3] .
- **Examples for oxidizing drugs:**
  1. Antibiotics: sulfonamides, trimethoprim
  2. Antimalarial: Primaquine

Neonatal methemoglobinemia

- **Methemoglobin:** is an oxidized form of hemoglobin that has a decreased affinity for oxygen → **tissue hypoxia.**
- **Epidemiology:** infants under 6 months of age are particularly prone to develop methemoglobinemia upon exposure to some oxidizing drugs

[3] babies with G6PD deficiency will not have glutathione system (antioxidant system). So if the baby expose to oxidant drugs he will get oxidant stress → RBCs hemolysis → ↑ bilirubin which will cross BBB → kernicterus (brain damage that happen to infant with jaundice)

Drugs & Lactation

Drugs contraindicated during lactation

- **Only few drugs are totally contraindicated:**
  - Anticancer drugs e.g. (Doxorubicin, cyclophosphamide, methotrexate) they will cause cytotoxicity and neutropenia
  - Radiopharmaceuticals e.g. radioactive iodine (If I have to do it for diagnose purpose, she has to stop the breastfeeding)
  - CNS acting drugs: amphetamine, heroin, cocaine (lipid soluble)
  - Immunosuppressants e.g. cyclosporine[4]
  - Alcohol[4] & Lithium (high milk to plasma ratio)[4]
  - Chloramphenicol (bone marrow suppression)[4]
  - Atenolol **& Sotalol, because their action is very very effective and may cause neonatal bradycardia and hypotension**
  - Potassium iodide (thyroid effect)[4]
  - Ergotamin (for migraine headaches) which may cause vomiting, diarrhea, convulsion in infants[4]
  - Tobacco smoke: nicotine can cause vomiting, diarrhea and restless for the baby, decreased milk production & increase respiratory and ear infection[4]

Drugs can suppress lactation

- **These drugs reduced prolactin Without harmful effects**
  - Levodopa (dopamine precursor)
  - Bromocriptine (dopamine agonist).
  - Estrogen, combined oral contraceptives that contain high-dose of estrogen and a progestin.
  - Androgens
  - Thiazide diuretics

Drugs can augment (increase) lactation

- **Dopamine antagonists**: they stimulate prolactin secretion galactorrhea
  - Metoclopramide (antiemetic) the only drug which we can clinically use to increase milk production, unlike the other drugs
  - Domperidone (antiemetic)
  - Haloperidol (antipsychotic)
  - Methyl dopa (antihypertensive drug)
  - Theophylline (used in asthma)

[4] Only female slides

Drugs & Lactation

Antibiotics	Penicillin Ampicillin amoxicillin	• No significant adverse effect, but mostly cause allergic reaction, diarrhea
	Cephalosporin	• No significant adverse effect • Alterations to infant bowel flora
	Macrolides: Erythromycin Clarithromycin	
Sedative/ hypnotics	Barbiturates (phenobarbitone)	• Lethargy, sedation, poor suck reflexes with prolonged use or chronic basis.
	Benzodiazepines Diazepam Lorazepam	• Single use of low doses is probably safe. • Lethargy, sedation in infants with prolonged use or chronic basis.
Antidiabetics	Insulin	• Safe
	Oral antidiabetics	• Compatible during breastfeeding
Analgesics	Paracetamol	• Safe
	Ibuprofen	• Compatible during breastfeeding
Antithyroid	Propylthiouracil Carbimazole Methimazole	• May suppress thyroid function in infants. • Propylthiouracil should be used rather than carbimazole or methimazole. Because Propylthiouracil is high protein binding.
Anticoagulants	Heparin	• 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	• Preferable over others • Compatible with breastfeeding • Amounts entering breast milk are not sufficient to produce adverse effects • Infants must be monitored for CNS depression

Drugs & Lactation

Oral contraceptives	Progestin Only Pills or mini-pills	• Preferred for birth control
Antidepressants[4]	Selective Serotonin Reuptake Inhibitor (SSRI)[4]	• Paroxetine is the preferred SSRI in breastfeeding women[4].
Antihistaminics[4]	Non-sedating antihistaminics[4]	• E.g. Loratidine[4]

Drugs should be avoided during lactation		
Antibiotecs	Quinolones	• Theoretical risk of athropathies (joint disease) • should be avoided
	Chloramphenicol	• Gray baby syndrome (avoid)
	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
Antidiabetics	Metformin	• Avoid due to lactic acidosis
Analgesics	Aspirin	• Avoid due to theoretical risk of Reye's syndrome
Oral contraceptives[5]	Estrogens Containing Pills	• Avoid it. • Estrogen ↓ milk quantity
Antithyroid	Potassium iodide	• Contraindicated
	Iodine (radioactive)	• Permanent hypothyroidism in infant • Breast-feeding is contraindicated
Anticonvulsants	Lamotrigine	• Avoid it doesn't cause any problem, but it has ↓ therapeutic index could cause toxicity very fast

[5] Non hormonal methods should be used

[4] Only female slides

Drugs & lactation

Drugs should be avoided during lactation		
Antihistaminics[4]	Sedating antihistaminics[4]	• Diphenhydramine (avoid)[4]
Cytotoxic drugs[6]		• Breast feeding should be avoided[6]
	Lithium[6] & alcohol	• Large amounts can be detected in milk (avoid)[6]
CVS drugs[6]	Atenolol[6]	• Risk of bradycardia and hypoglycemia (avoid)[6]

Drugs of Choice in Lactation

Antibiotics	Safe	• Cephalosporins, penicill
	Avoid	• chloramphenicol, quinolones, sulphonamides and tetracyclines
Antidiabetics	Safe	• Insulin – oral antidiabetics
	Avoid	• Metformin
Anticoagulants	Safe	• Heparin, warfarin
Analgesics	Safe	• Acetaminophen (paracetamol)
Antithyroid	Safe	• Propylthiouracil are preferable over others
Anticonvulsants	Safe	• Carbamazepine, phenytoin
Oral contraceptives		• Progestin only pills or minipills are preferred for birth control
Anti-asthmatic	Safe	• Inhaled corticosteroids, prednisone

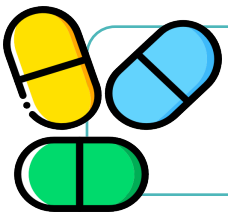
[4] only female slides
[6] Only male slides

Summary for Choices of Drugs

- Drugs known to have serious toxic effects in adults are avoided (only female slides)
- **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 with first pass metabolism. Because its concentration in maternal blood will be low so its concentration in milk will be low.
- **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

- Do not guess
- Use the following sources:
  - ✓ Use medication and mothers' milk (www.iBreastfeeding.com)
  - ✓ Use lactmed or toxnet (http://toxnet.nlm.nih.gov)[7]

[7] a free online database with information on drugs and lactation, is one of the newest additions to the National Library of Medicine's TOXNET system, a Web-based collection of resources covering toxicology, chemical safety, and environmental health.

Summary

Pharmacokinetics changes in pediatrics

- Higher gastric pH
- Lower rate of metabolism due to immaturity of liver enzymes.
- Renal clearance is less efficient: (↓Renal blood flow- ↓ GFR).
- Higher concentrations of free drug
- Higher percentage of body water
- Premature babies have very limited capacity for metabolism and excretion.

Drugs contraindicated during lactation		Drugs that can suppress lactation(reduce prolactin)	Drugs that can augment lactation(Dopamine antagonists)
• Anticancer drugs: Doxorubicin, cyclophosphamide, methotrexate. • Radiopharmaceuticals: Radioactive iodine. • CNS acting drugs: amphetamine, heroin, cocaine. • Immunosuppressants: Cyclosporine.	• Alcohol &Lithium. • Chloramphenicol. • **Atenolol**. • Potassium iodide . • Ergotamine. • Tobacco Smoke.	• Levodopa . • Bromocriptine. • Estrogen, combined oral • contraceptives that contain high-dose of estrogen and a progestin. • Androgens. • Thiazide diuretics .	• Metoclopramide . • Domperidone . • Haloperidol . • Methyl dopa . • Theophylline .

Drugs should be avoided during lactation

Quinolones	• risk of athropathies
Chloramphenicol	• Gray baby syndrome (avoid)
Tetracycline	• possible risk of teeth discoloration.
(co-trimoxazole)	• hyperbilirubinemia - neonatal jaundice
Metformin	
Asprin	• Risk of Reye's syndrome
Estrogens Containing Pills	
potassium iodide Iodine (radioactive)	
Lamotrigine	

Drugs of choice in lactation

Antibiotics	Cephalosporins, penicillins
Antidiabetics	Insulin – oral antidiabetics
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

MCQs

Q1: Which of the following drug's characteristics will lead to appearance of a drug in the milk of breastfeeding mother ?
A- Acidic drug. B- Drug with Large distributed volume. C- Highly ionized drug. D- Alkaline drug.

Q2: Which of the following drug's characteristics will be considered when we look for the safest drug for breastfeeding mother?
A- Acidic drug. B- Drug with Low distributed volume. C- non-ionized drug. D- Alkaline drug

Q3: Which of the following is the proper time for breastfeeding mother to take medication ?
A. 1 hour before nursing her child. B. At the same time of nursing her child. C. Just After nursing her child. D. It does not matter when.

Q4: Breastfeeding mother has baby with G6PD deficiency. The mother get UTI and took antibiotic for that. Two days later, her baby develops jaundice. What drug most likely was taken by the mother to cause this complication in the child ?
A. Penicillin. B. Ciprofloxacin. C. Co-trimixazole. D. Doxycycline.

Q5: Which of the following antibiotic can cause grey baby syndrome ?
A. Doxycycline. B. Ciprofloxacin. C. Co-trimixazole. D. Chloramphenicol.

Q6: Which of the following is considered as compatible/safe drug with breastfeeding mother ?
A. Methotrexate B. Warfarin C. Phenobarbitone. D. Lithium. E. Lamotrigine

Q7: Which one of the following drugs should be avoided in breastfeeding mother?
A. Heparin. B. Warfarin. C. methyl dopa. D. Lithium. E. Acetaminophen.

Q8: Which one of the following drugs could be harmful to the baby during breastfeeding in chronic basis ?
A. Valproic acid. B. Propylthiouracil. C. Ibuprofen. D. mini-pills. E. Phenobarbitone.

Q9: Which of the following beta blockers is highly contraindicated in lactating women ?
A. Propranolol. B.Timolol. C. Nadolol. D. Atenolol.

Q10: Which of the following may lead to hyperbilirubinemia in babies ?
A. Breastfeeding mother who is taking a drug with high binding capacity to albumin.
B. Breastfeeding mother with malaria who is taking Primaquine as anti-malaria agent.
C. Breastfeeding mother with UTI who is taking sulfonamides as anti-bacterial agent.
D. All of them.

Q11: Which of the following can reduce the volume of milk in lactating mother ?
A. mini-pills . B. Metoclopramide C. Haloperidol. D. Estrogen.

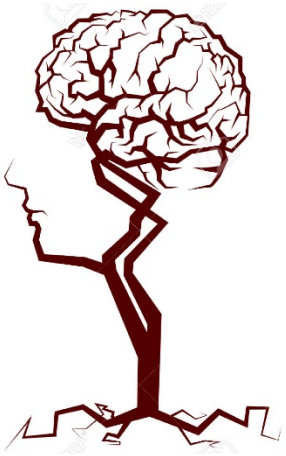
Q12: Which of the following can suppress lactation in breastfeeding mother ?
A.Theophylline. B. Metoclopramide C. Bromocriptine . D. Domperidone.

Q13: Which of the following can suppress lactation in breastfeeding mother ?
A. Metoclopramide B. Levodopa. C. . Methyl dopa. D. Phenothiazine.

Q14: Which of the following drugs can augment lactation in breast feeding mother ?
A. Bromocreptine. B. Metoclopramide. C. Testosterone. D. Estrogen.

Q15: Which of the following drugs can augment lactation in breast feeding mother ?
A.Hydrochlorothiazide. B. Levodopa. C. . Methyl dopa. D. Bromocriptine .

1) D. 2) A. 3) C. 4) C. 5) D. 6) B. 7) D. 8) E. 9) D. 10)D. 11)D. 12)C. 13)B. 14)B. 15)C.



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References :

1- 436 doctor’s slides and notes

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