



Drugs affecting breast milk and lactation

Objectives:

- **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.

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Drug's name | Doctors' notes | Important | Extra

« قل سيروا في الأرض فانظروا كيف بدأ الخلق »

Mind Map

Drugs affecting breast milk and lactation

Drugs of choice in lactation

Antibiotics:
(Cephalosporins, penicillins)

Antidiabetics:
(Insulin, oral antidiabetics.
Avoid: metformin)

Anticoagulants :
(Heparin, warfarin)

Analgesics:
(Acetaminophen (paracetamol))

Antithyroid drugs
(Propylthiouracil)

Anticonvulsants:
(Carbamazepine, phenytoin)

Oral contraceptives
(Progestin)

Antiasthmatics:
(Inhaled corticosteroids, prednisone)

Drugs contraindicated during lactation

Anticancer drugs:
(Doxorubicin, cyclophosphamide, methotrexate)

Radiopharmaceuticals: (radioactive iodine)

CNS acting drugs:
(amphetamine, heroin, cocaine)

Lithium

Chloramphenicol

Atenolol

Potassium iodide

Drugs that can suppress lactation

Levodopa
(dopamine precursor)

Bromocriptine
(dopamine agonist).

Estrogen, combined oral contraceptives that contain high-dose of estrogen and a progestin.

Androgens

Thiazide diuretics

Drugs that can augment lactation

Dopamine antagonists:
(Metoclopramide, domperidone, Haloperidol, Methyl dopa, Theophylline)

Lactation

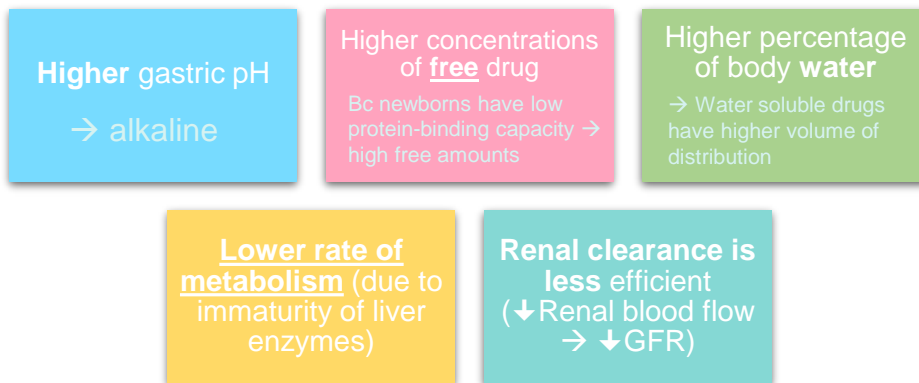
- **Breast feeding** is very important because breast milk is the healthiest form of milk for babies.
- It provides the baby with immunoglobulins (**IgA, IgM**) that are essential for protection against gastroenteritis.

Drugs 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.
Most of the drugs are safe during lactation, bc the ability of the drug to be transported & excreted in the milk is very limited.

Pharmacokinetic changes in pediatrics- newborn

Why does newborn have limited capacity?



- **Premature babies*** have very **limited capacity for metabolism and excretion**.
* born too early, before 37 weeks of gestational age.

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

	Neonate	Adult
Gastric acid output (mEq/10kg/hr)	0.15 ↓ → ↑ pH	2
Gastric emptying time (min)	87 ↑	65
Total body water (% of body weight)	78 ↑ <small>يحدد إذا الدرق بيروح ناحية H₂O أو لا</small>	60
Adipose tissue (% of b.wt.)	12 ↓ <small>يحدد إذا الدرق بيروح ناحية Fat أو لا</small>	12-25
Serum albumin (gm/dL)	3.7 ↓	4.5
Glomerular filtration rate (ml/min/m ²)	11 ↓ (very low)	70

Pediatric population are classified into:

الدكتور طمر هالجدول

Newborn		Infants	Children		Adolescent
Less than one month old		1 -12 months of age	1-12 years of age		13-18 years
Preterm neonates	Full-term neonates		Toddler (young child)	Older child	
Born before 38 weeks of gestational age	38-42 weeks of gestational age		1-5 years	6-12 years	

Factors controlling the passage of drugs into breast milk:

Factors related to <u>drugs</u>	<u>Maternal</u> factors	<u>Infant</u> factors
<ul style="list-style-type: none"> Molecular weight Lipid solubility Degree of ionization Drug pH Protein binding Oral bioavailability, T1\2 	<ul style="list-style-type: none"> Dose of drug Route of Administration Time of breast feeding Health status Maternal drug concentration 	<ul style="list-style-type: none"> Age Weight Health status

Factors related to **drugs**

❖ **Molecular weight:** The higher MW → the lower to be transported and vice versa.

- Very small molecules (< 200 Daltons) such as **alcohol**, **equilibrate rapidly between plasma and breast milk via the aqueous channels surrounding alveoli.**

لو عندي أم مدمنة الكحول وكانت تأخذ أثناء فترة الرضاعة مقدار معين، **نفس المقدار** هذا بيترفض له الجنين من الحليب! = 100% transfer capacity

- Large molecules drugs (>800 Daltons) are less likely to be transferred to breast milk than low molecular weight. → it is better to take high MW during breast-feeding women.
- 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.

أهم مرحلة للرضاعة هي أول رضاعة بعد الولادة. ليه؟ لأن الارتفاع permeability of epithelial cells of breast alveoli is high فقي هذي الفترة لازم نأخذ حذرنا بالنسبة للhigh permeability مقارنة بما بعد الأسبوع الأول فيما يخص الأدوية.

❖ **Lipid solubility of the drug:**

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

❖ **Degree of ionization:** The more degree of ionization (polar) → the less transfer to the milk

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

❖ **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.**

من سنة أولى متفقين إن strong base or acid can't be used as a medication

ليه؟ لأنهم يعملوا irritation ولما يصيروا strong بيصير لهم درجة تأين عالية، وهذا الشيء ماهو كويس لأنه مراح يصير لهم absorption (إذا أخذته الجاي) لو عندي دواءين يعطيهن للمرضع، واحد منهم weak acidic والثاني weak basic. أيهم أعطي؟ أكيد الacidic! ليه؟ لأنه تركيزه بيكون قليل في الحليب (الشرح في السلايد الجاي)

Factors related to **drugs** (cont.)

Maternal blood circulation

Plasma pH is 7.4

Alkaline drug

Lipid soluble = non-ionized form

Lipid soluble = non-ionized form

Acidic drug

Milk

pH is 7.2 (**More acidic**)

Ionized alkaline drug will be **captured**

صار كأنه polar = ماراح يقدر يرجع ☹️

Non-ionized acidic drug will **diffuse back**

Non-ionized = lipid soluble

لما يلاقي الدواء وسط نفس وسطه، راح يصير له reabsorption (في حالتنا إذا كان الدواء حمضي والوسط اللي رايح له حمضي كذلك (الحليب) ، فراح يصير للدواء إعادة امتصاص، لكن لما يصير الدواء قاعدي، والوسط اللي رايح له حمضي، هنا بيتلاقى المتضادان ويحصل بينهم مضاربة وهم متشابهين مع بعض لما يطلعون من الجسم ويفكونا ☺️ هذا المبدأ نفسه مبدأ ال excretion of drugs in kidney في بلوك الرينال إذا نتذكرون.

❖ 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**

❖ Half life:

- Avoid the use of drugs with long half lives
- **Short half life ($t_{1/2}$) are preferable.** | Avoid drugs with long $T_{1/2}$
- **Oxazepam¹ vs Diazepam².** 1: short duration of action → ↓ the exposure of this drug to baby. 2: long duration of action

❖ Volume of distribution:

- Transfer of drug from maternal blood to milk is **low** with drugs that have **large volume of distribution (Vd)**. → The **higher the Vd** → The **lesser the transfer** to the milk

كيف طيب؟ لأن لما الأم تأخذ دواء له Vd عالي، فالدواء راح يتوزع في كل أنسجة الجسم وتركيزه في الدم قليل، فماراح يصير في الثدي إلا كمية بسيطة. لكن لو الدواء عنده low Vd، فماراح يروح ويتوزع على أنسجة الأم، ويصير تركيزه في الدم كثير، بالتالي اللي بيوصل للثدي كمية أكبر.

المحصلة:

الخصائص المفضلة للأدوية عشان ما يصير تركيزها عالي في الحليب:

1- High MW. 2- ionized. 3- Acidic. 4- highly bound to plasma proteins. 5- short $T_{1/2}$. 6- high Vd.

Factors related to **neonates**

Age & Health status

Body weight

Special cautions are required in :

- **Premature infants** → (born before 38 wks. of gestation). has very limited capacity to metabolize & excrete drugs. (born before 38 wks. of gestation)
- **Low birth weight**
- **Infants with G6PD deficiency.**
- **Infants with impaired ability to metabolize /excrete drugs e.g. hyperbilirubinemia**

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.

Factors related to **mother**

Time of breast feeding

It is “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 (if taken orally) to be cleared from the mother’s blood → drug concentration in milk will be **low**.

يعني إما إنها ترضعه وتأخذ دواها، أو تأخذ دواها وتقعده ٣-٤ ساعات بعدين ترضع ولدها.

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

نحاول نبتعد عن systematic administration (oral & injection)

Maternal drug concentration

Dose of the drug

أحيانا ما أقدر أغير في الجرعة، لأن لو غيرتها ممكن ما تعطيني التأثير اللي أبيه.

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 e.g. anti-epileptics, CNS depressants

Neonatal disorders caused by the transfer of maternal's drugs

Neonatal hyperbilirubinemia

- Premature infants or infants with inherited G6PD deficiency are susceptible to **oxidizing drugs** that can cause → hemolysis of RBCs → ↑ bilirubin (hyperbilirubinemia) → ↑ Kernicterus.
- G6PD? Enzyme found in the cell membrane of RBCs to prevent destruction by free radicals (has anti-oxidant effect). So when baby is already has ↓ G6PD → when he has oxidant drugs from mother's milk → results in hemolysis of RBCs.

Neonatal Methemoglobinemia

- Methemoglobinemia? When the iron bound to hemoglobin is in the ferric form (Fe^{3+}) instead of ferrous form (Fe^{2+}) → methemoglobin can't hold O_2 .
- 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.

❖ Examples for oxidizing drugs:

- Antibiotics: **sulfonamides** (any sulfa medication is C.I.), **trimethoprim**
- Antimalarials: **Primaquine**

Drugs & Lactation

1- Drugs contraindicated **during** lactation

Only few drugs are totally contraindication

Drug	Anticancer drugs	Radiopharmaceuticals	CNS acting drugs
example	<ul style="list-style-type: none"> • Doxorubicin • Cyclophosphamide (C.I in pregnancy also) • Methotrexate 	<ul style="list-style-type: none"> • Radioactive iodine 	<ul style="list-style-type: none"> • Amphetamine • Heroin • Cocaine
Drug	Lithium Its problem is the same of Alcohol, its transfer capacity is 100%	<u>Chloramphenicol</u> Bc baby doesn't have glucuronyl transferase → develops hypoxia	Atenolol Beta-blocker, C.I bc its conc. is high in the milk
Drug	Potassium iodide bc its conc. is high in the milk		

Drugs & Lactation (cont.)

2- Drugs that can **suppress** lactation

These drugs reduce prolactin, without harmful effect.

Drug	Levodopa "dopamine precursor"	Bromocriptine "dopamine agonist"	Estrogen, combined oral contraceptives that contain high-doses of estrogen and a progestin
Drug	Androgens	Thiazide diuretics	

3- Drugs that can **augment** lactation

Dopamine antagonists: they stimulate prolactin secretion → galactorrhea e.g.:

Drug	Metoclopramide and Domperidone "antiemetic"	Haloperidol "antipsychotic"	Methyldopa "antihypertensive drug"
Drug	Theophylline "used in asthma"		

Antibiotics

الأدوية المذكورة في هذا الجدول، نفس حالة pregnancy التي ينفع مع الحامل ينفع مع المرضع

Drug	Penicillins: Ampicillin, Amoxicillin	Cephalosporins	Macrolides: Erythromycin, Clarithromycin
Inf.	<ul style="list-style-type: none"> ✓ No significant adverse effect. Can cause: allergic reactions, diarrhea (not significant) 	<ul style="list-style-type: none"> ✓ No significant adverse effect can cause: alterations to infant bowel flora. <ul style="list-style-type: none"> ○ Mother takes them if she can not take penicillins. 	
drug	Quinolones	Chloramphenicol	Tetracyclines
Inf.	<ul style="list-style-type: none"> ✗ Theoretical risk of arthropathies ✗ Should be avoided 	<ul style="list-style-type: none"> ✗ "Gray baby" syndrome → avoid خصوصًا أثناء السنة الأولى من الولادة 	<ul style="list-style-type: none"> ✗ Absorption by the baby is probably prevented by chelation with milk calcium. → Avoid due to possible risk of teeth discoloration.
drug	Sulfonamides (co-trimoxazole)		
Inf.	<ul style="list-style-type: none"> ✗ Hyperbilirubinemia -neonatal jaundice → Should be avoided in premature infants or infants with G6PD deficiency. (oxidizing drugs) 		

Sedatives/Hypnotics

Barbiturates (Phenobarbitone)	Benzodiazepines, Diazepam, Lorazepam
<p>✗ Lethargy, sedation, poor suck reflexes with prolonged use.</p>	<p>✗ Single use of low doses: Mostly <u>safe</u>.</p> <p>✗ Prolonged use: Lethargy, sedation in infants.</p>

Antidiabetics

نقدر نستخدم مع المرضع oral hypoglycemic أو insulin injection لكن الحامل بس إنسولين!!

Insulin	Oral Antidiabetics	Metformin
<p>✓ Safe</p>	<p>✓ Compatible = it's ok to use</p>	<p>✗ Avoid due to lactic acidosis (Rare)</p>

Analgesics

Paracetamol	Ibuprofen	Aspirin
<p>✓ Safe</p>	<p>✓ Compatible</p>	<p>✗ Avoid due to theoretical risk of Reye's syndrome</p>

Anti-convulsants

Carbamazepine	Phenytoin	Valproic Acid	Lamotrigine
<p>✓ Preferable over others, Compatible with breastfeeding</p>	<p>○ Amounts entering breast milk are not sufficient to produce adverse effect.</p>	<p>○ Infants must be monitored for CNS depression</p>	<p>✗ AVOID</p>

Anticoagulants

Heparin	Warfarin
<p>✓ Safe, not present in breast milk.</p>	<p>✓ can be used, very small quantities found in breast milk, monitor the infant's prothrombin time during treatment. (warfarin is C.I in pregnant women)</p>

Antithyroid drugs

Propylthiouracil*, Carbimazole, Methimazole, Potassium iodide

- May suppress thyroid function in infants.
- ✓ **Propylthiouracil** should be used rather than **carbimazole** or **methimazole**.

Everything else (Cont.)

Cytotoxic Drugs	CVS drugs (Atenolol)
X Avoid breast feeding.	X Risk of bradycardia and <u>hypoglycemia</u> , AVOID
Lithium	Antidepressants: SSRI
X LARGE amounts can be detected in milk, AVOID	✓ Paroxetine is the preferred SSRI in breastfeeding women
Oral Contraceptives	
✓ Non-Hormonal method should be used. X Avoid <u>estrogen</u> containing pills: Estrogen = ↓ Milk quantity ✓ Progestin only pills (mini pills *) are preferred for birth control → they do not have adverse effects on lactation, although there is still controversy regarding early use in breastfeeding women.	Iodine (<u>Radioactive</u>)
	X <u>Permanent hypothyroidism</u> in infant, Breast feeding is <u>contraindicated</u> .

Choice of Drug (slides summary):

- ROUTE of administration: Topical, local, inhalation, instead of oral.
- SHORT acting
- HIGHLY protein bound
- LOW lipid solubility
- HIGH molecular weight
- POOR oral bioavailability → will not absorbed well → its conc. is not high.
- NO active metabolites
- WELL-STUDIED in infants

General Considerations:

اقرأوها بس

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:

- [Medication and Mothers' Milk](#)
- Lactmed or [toxnet](#)

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 -1

class of drugs	Drugs contraindicated during lactation	Drugs that can suppress lactation (reduce prolactin)	Drugs that can augment lactation
Drugs	<ul style="list-style-type: none"> • Anticancer drugs: Doxorubicin, cyclophosphamide, methotrexate. • Radiopharmaceuticals: radioactive iodine. • CNS acting drugs: Amphetamine, Heroin, Cocaine. • Lithium • Chloramphenicol • Atenolol • Potassium iodide 	<ul style="list-style-type: none"> • Levodopa (dopamine precursor) • Bromocriptine (dopamine agonist). • Estrogen, (combined oral contraceptives that contain high-dose of estrogen and a progestin.) • Androgens • Thiazide diuretics 	<ul style="list-style-type: none"> ○ Dopamine antagonists: (stimulate galactorrhoea) • Metoclopramide (antiemetic) • Domperidone (antiemetic) • Haloperidol (antipsychotic) • Methyldopa (antihypertensive drug) • Theophylline (used in asthma)

class of drugs	Antibiotics
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Drugs	<ul style="list-style-type: none"> • Cephalosporins, Macrolides (erythromycin clarithromycin): alterations to infant bowel flora. • Penicillins, Ampicillin, amoxicillin: allergic reactions, diarrhea. • Quinolones: Theoretical risk of arthropathies (avoid). 	<ul style="list-style-type: none"> • Chloramphenicol: “Gray baby” syndrome (avoid) • Tetracyclines: Absorption by the baby is prevented by chelation with milk calcium. (Avoid “risk of teeth discoloration”). • Sulfonamides (co-trimoxazole): hyperbilirubinemia -neonatal jaundice-avoid in <u>premature infants</u> or infants with <u>G6PD deficiency</u>.
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class of drugs	Sedative/hypnotics
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Drugs	<ul style="list-style-type: none"> • Barbiturates (phenobarbitone): Lethargy, sedation, poor suck reflexes with <u>prolonged use</u>. • Benzodiazepines (Diazepam, Lorazepam): Single use of low doses is safe. Lethargy, sedation with <u>prolonged use</u>.
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class of drugs	Antidiabetics
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Drug	<ul style="list-style-type: none"> - Insulin: safe, - Oral antidiabetics: compatible, - Metformin: avoid “lactic acidosis”
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class of drugs	Analgesics
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Drug	<ul style="list-style-type: none"> - Paracetamol: safe, - Ibuprofen: compatible, - Aspirin: avoid “Reye's syndrome”
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Class of drugs	Oral contraceptives
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Class of drugs	<ul style="list-style-type: none"> - Non hormonal method should be used, - Avoid estrogens containing pills, - Estrogens ↓ milk quantity, - Progestin <u>only</u> pills or mini pills for <u>birth control</u>.
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Summary -2

class of drugs	Antithyroid drugs	
Drug	<ul style="list-style-type: none"> • Propylthiouracil, Carbimazole, Methimazole, potassium iodide: - <u>suppress</u> thyroid function in <u>infants</u>. –Propylthiouracil: better “ use it “ 	
class of drugs	Anticoagulants	
Drug	<ul style="list-style-type: none"> • Heparin: Safe, <u>not</u> present in breast milk. 	<ul style="list-style-type: none"> • Warfarin: can be used, monitor the infant's prothrombin time during treatment.
class of drugs	Anticonvulsants	
Drug	<p>(Preferable over others):</p> <ul style="list-style-type: none"> - Carbamazepine: Compatible, - Phenytoin: no adverse effect. - Valproic acid: <u>monitor</u> Infants for CNS depression -Lamotrigine: avoid. 	
class of drugs	Antidepressants	
Drug	<ul style="list-style-type: none"> • SSRI: (Paroxetine) is the <u>preferred</u> SSRI in breastfeeding women. 	
	Other	
Drug	<ul style="list-style-type: none"> - Iodine (radioactive): <u>hypothyroidism</u> in infant Avoid breast feeding - CVS drugs (Atenolol): bradycardia and hypoglycemia (avoid) 	<ul style="list-style-type: none"> - Cytotoxic drugs: Avoid breast feeding - Lithium: Large amounts can be detected in milk (avoid).
class of drugs	Drugs of choice in lactation	
Drug	<ul style="list-style-type: none"> • Antibiotics: Cephalosporins, penicillins <u>are safe</u>, Avoid: chloramphenicol, quinolones, sulphonamides and tetracyclines , • Antidiabetics: Insulin – oral antidiabetics <u>are safe</u>, Avoid: metformin, • Anticoagulants: Heparin – warfarin, • Analgesics: Acetaminophen (paracetamol), • Antithyroid drugs: propylthiouracil is <u>preferable</u> over others, • Anticonvulsants: Carbamazepine – phenytoin, • Oral contraceptives: Progestin <u>only</u> pills or mini pills are <u>preferred</u> for birth control, • Antiasthmatics: <u>Inhaled</u> corticosteroids – prednisone. 	

MCQs

1- Which one of the following drugs requires the infant to be regularly monitored for CNS depression?

- A. Valporic acid
- B. Lamotrigine
- C. Phenytoin
- D. Carbamazepine

2- Which of the following is true for pediatric pharmacokinetics?

- A. Low concentrations of free drug
- B. Lower rate of metabolism
- C. Lower percentage of body water
- D. Lower gastric pH

3- Acidic drugs diffuse through maternal circulation into the milk?

- A. True
- B. False

4- Lactating mother should take medication:

- A. after nursing and 3-4 hours before the next feeding
- B. after nursing and 1-2 hours before next feeding
- C. 30 min before nursing
- D. 45 min - 1h before nursing

5- Neonate with hyperbilirubinemia should avoid which of the following:

- A. Doxorubicin
- B. methotrexate
- C. Sulfonamides
- D. Cyclophosphamide

6- Which of the following is contraindicated during lactation?

- A. Domperidone
- B. radioactive iodine
- C. Metoclopramide
- D. All are fine

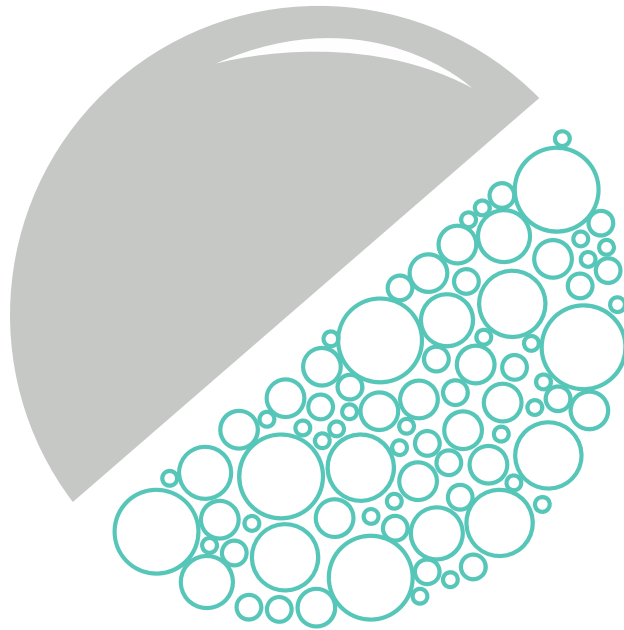
7- Which of these medicine should you avoid while breastfeeding?

- A. Paracetamol
- B. Progestin only contraceptives
- C. Atenolol
- D. Carbamazepine

8- Which route of drug administration is not preferred while breastfeeding?

- A. Topical
- B. Inhalation
- C. Oral
- D. Dermal patches

Thank you for checking our team!



Pharmacology 435

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Sources:

1. 435's slides.