Drug Use During Lactation

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Pharmacology

Drugs in Lactation

- **Breast milk is the best form of nutrition for young infants.**
- **Mothers should breast feed exclusively for 6 months, and continue until at least 12 months while other foods are introduced.**
- **Breast milk provides all the energy and nutrients required for the first 6 months of life.**

Drugs in Lactation

Breast feeding provides:

1) **Protection of the infant against gastric, respiratory, and urinary tract infections.**
2) **Reduction in the rate of obesity, and juvenile-onset diabetes mellitus.**
3) **Reduction in the rate of atopic diseases.**

- **Adults who were breastfed as infants have lower blood pressure and lower cholesterol levels.**

Drugs in Lactation

Maternal benefits of beast feeding include:

1. **Reduced risk of developing pre-menopausal breast cancer**
2. **Strengthening of the mother-infant bond.**

Drugs in Lactation

- **Breastfeeding mothers frequently require treatment with drugs.**
- **There are few contraindications to breast feeding.**
- **Some mothers may self-medicate with over-the-counter medications, nutritional supplements and herbal medicines.**

Drugs in Lactation

- **Nursing mothers need advice about safe drug use during lactation to protect the infant from drug-related adverse effects, and to allow necessary maternal treatment.**

Transfer of Drugs into Breast Milk

- Most drugs pass to breast milk to some extent, but breastfeeding may be continued in most cases.
- The drug dose ingested by the infant via breast milk only rarely cause adverse effects.
- Almost all drugs enter milk by passive diffusion of un-ionized, protein un-bound drug through the lipid membrane of the alveolar cells of the breast.

Transfer of Drugs into Breast Milk

- **Factors affecting rate and extent of passive diffusion include maternal plasma drug level, physiological differences between plasma and milk, and physicochemical properties of the drug.**
- **Milk differs from blood in having lower pH (ranges from 6.8 – 7.0 vs 7.4 in serum), less buffering capacity, and higher fat content.**

Transfer of Drugs into Breast Milk

Drug parameters affecting the extent of transfer into milk:

1. **pKa:**

- **It determines drug ionization at a given pH.**
- **Highly ionized drugs tend NOT to concentrate in milk.**
- **For basic drugs (erythromycin), a greater fraction will be ionized at an acidic pH, so that the milk compartment tends to trap weak bases.**

Transfer of Drugs into Breast Milk

- **Acidic drugs (penicillin) are more ionized at higher pH values and will be trapped in the plasma compartment.**
- **Drugs with higher pKa values generally have higher milk/plasma ratios.**

2. **Protein binding:**

- **Drugs that are highly bound to plasma proteins (warfarin) are likely to be retained in the plasma, because there is lower protein content in milk.**

Transfer of Drugs into Breast Milk

- **Milk concentration of highly plasma protein-bound drugs is usually low.**

3. **Lipophilicity:**

- **Water-soluble drugs will NOT effectively cross the alveolar epithelium of the breast.**
- **CNS-active drugs usually cross to breast milk.**

4. **Molecular weight:**

- **Drugs with low molecular weight (<200) readily pass into the milk through small pores in the cell wall of alveolar cells.**

Transfer of Drugs into Breast Milk

- **Drugs with higher molecular weights cross cell membranes by dissolving in the lipid layer.**
- **Protein molecules (very large molecular weights > 6000 daltons) are virtually excluded from milk.**

Transfer of Drugs into Breast Milk

- **Therefore, drugs that pass minimally to breast milk would be:**

1) **an acidic drug.**
2) **a drug with high plasma protein binding.**
3) **a drug with low-to-moderate lipophilicity.**

(most NSAIDs)

Transfer of Drugs into Breast Milk

- **Therefore, drugs that pass significantly to breast milk would be:**

1) **A basic drug**
2) **A drug with low plasma protein binding**
3) **A dug with relatively high lipophilicity (sotalol).**

Transfer of Drugs into Breast Milk

- In the first few days of life, large gaps exist between alveolar cells that permit enhanced passage of drugs into milk.
- By the end of the first week, the gaps close under the influence of prolactin.
- Colustrum is secreted in the first 2 days after birth and has high amounts of immunoglobulins, maternal lymphocytes, and maternal macrophages.

Transfer of Drugs into Breast Milk

- Greater amounts of drugs are present in colustrum but the amounts received by infants are low because of the low volume of colustrum produced.
- Some drugs are pumped actively into breast milk, such as iodides, which pass into milk with high concentration.

Assessing the Risk to the Infant

Many factors should be considered:

1. **Inherent toxicity of the drug: Antineoplastic drugs, radionuclides, and iodine-containing compounds would be of concern.**
2. **Multiple maternal therapy with drugs having similar adverse effects (anticonvulsants, and psychotropic drugs) will increase the risk for the infant.**

Assessing the Risk to the Infant

3. **Active metabolites (benzodiazepines) may prolong infant drug exposure and lead to drug accumulation.**
4. **Drugs with long half-lives (fluoxetine) may be problematic.**
5. **Gestational age: premature infants are more susceptible because of low clearance.**
6. **Maternal drug regimen: single doses or short courses have lower risk than chronic therapy or multiple medications.**

Reducing Risk to the Breastfed Infant

Strategies to reduce the risk of drugs in breast fed infants:

1. **Select medication considered safe for use in infants.**
2. **Give the maternal dose immediately after the infant has been fed, to avoid feeding at peak concentration of the drug in milk (if possible depending on frequency of feeding).**

Reducing Risk to the Breastfed Infant

3. If the mother is receiving a single dose of a hazardous material (radiopharmaceuticals), avoid breast feeding and resume after a reasonable washout period (5 half-lives). If the half-life is long, the washout period will be very long.
4. If the mother is using a once-daily medication, administration before the infant's longest sleep period may be advised to increase the interval to next feeding.

Reducing Risk to the Breastfed Infant

5. Breastfeeding mothers should avoid self-medication.
6. When drug use is indicated, the lowest effective dose should be used for the shortest possible period of time.
7. Simplify maternal regimen as much as possible.
8. New drugs are best avoided if a therapeutic equivalent is available for which data on safe use during lactation is available.

Reducing Risk to the Breastfed Infant

9. Infants exposed to drugs through breast milk should be monitored for adverse effects.
10. Select drugs with short half-lives and high protein binding to reduce accumulation.
11. For drugs taken multiple times per day, administration immediately after breast feeding provides the longest interval of back diffusion of the drug from breast milk into mother's serum.

Reducing Risk to the Breastfed Infant

12. During short-term drug therapy, and if the medication is NOT compatible with breastfeeding, the mother can pump milk out and discard it to preserve here milk-producing capability.

- Information regarding drug use during breastfeeding can be obtained from www.toxnet.nlm.nih.gov

Special Situations

Neonates and premature Infants:

1. **They are at greater risk of developing adverse effects to drugs after exposure via breast milk.**
2. **Gastric emptying time is prolonged and may alter drug absorption.**
3. **Protein binding is decreased.**
4. **Total body water is higher.**
5. **Renal function is limited.**
6. **Conjugation capacity is deficient (oxazepam).**

Special Situations

Glucose-6-phosphate dehydrogenase deficiency:

1. **It makes erythrocytes more susceptible to oxidative stress which results in hemolysis.**
2. **Only small amounts of the drug in breast milk are needed to produce hemolysis.**
3. **Breastfeeding should be avoided and alternative drugs should be used if the infant is G6PD deficient.**

Special Situations

Recreational Drug Use:

1. **Substances such as cannabis, LSD, and cocaine should be avoided during breastfeeding.**
2. **Chronic or heavy consumers of alcohol should NOT breastfeed.**

- **High intake of alcohol in breastfeeding mothers:**

a) **decrease milk let down.**

b) **disrupt nursing.**

c) **causes infant sedation, fluid retention, and hormone imbalances in infants.**

Special Situations

3. **Nicotine decreases basal prolactin production. Mothers should be encouraged NOT to smoke whilst breastfeeding.**
4. **Caffeine appears in breast milk rapidly after maternal intake. ~ 10 or more cups of coffee per day by the mother produce fussiness, jitteriness, and poor sleep patterns in breast fed infants.**

- **Preterm and newborn infants metabolize caffeine slowly and are at increased risk.**

Drug Effects on Lactation

1. **Drugs that affect dopamine activity are the main cause of effects on milk production.**

   A. Dopamine agonists (cabergoline) decrease milk production.

   B. Dopamine antagonists (domperidone) increase milk production.

2. **Early postpartum use of estrogens may reduce the volume of milk.**

- **Milk production can be abolished by the use of estrogens or oral contraceptives.**

Drug Effects on Lactation

- **Breast milk production can be increased by metoclopramide (10 mg po, 3 times daily for 7-14 days) if nonpharmacological means are ineffective. It stimulates prolactin secretion.**

Drug Effects on Lactation

Table 1. Pharmacological galactagogues

Oral pharmacological galactagogue	How it might work	Harms	Reference(s)
Domperidone	Peripherally acting dopamine D2-receptor antagonist, increases prolactin release from the pituitary gland	Headaches, somnolence, abdominal pain, diarrhoea. Increased risk of cardiac problems if history of prolonged Q-T interval, especially at high doses	Anderson 2013, Barone 1999, Doggrell 2014, Forinash 2012, Hale 2007, Zuppa 2010
Metoclopramide	Increases prolactin levels by anti-dopaminergic effects	Crosses the blood brain barrier causing restlessness, drowsiness, fatigue, depression and involuntary body movements	Anderson 2013, Forinash 2012, Hale 2007, Zuppa 2010

Drug Effects on Lactation

Table 2. Botanical galactagogues

Oral botanical galactagogue	How it might work	Harms	Reference(s)
Fenugreek (*Trigonella foenum-graecum*) نبات الحلبة	Increases milk flow by its phytoestrogens and diosgenin contents Stimulates sweat production, which would enhance milk secretion because the breast is a kind of sweat gland May stimulate milk production through dopamine receptor antagonism	Digestive upset, loose stools, light headedness, maple smell in the urine and sweat, mild allergic reaction. Possible peanut allergen cross sensitivity	Abascal 2008, Bingel 1994, Bruckner 1993, Capasso 2009, Humphrey 2007, Low Dog 2009, MacIntosh 2004, Mortel 2013, Romm 2010
Blessed thistle (*Cnicus benedictus*)	Stimulates the flow of blood to the mammary glands	Increased risk of bleeding	Abascal 2008, Bingel 1994, Zapantis 2012

Torbangun leaves (*Coleus amboinicus* Lour)	May stimulate proliferation of secretory mammary cells	Hypoglycaemia and stimulation of the thyroid gland	Bingel 1994, Zapantis 2012, Mortel 2013
Goat's rue (*Galega officinalis*)	Contains galegin, a precursor to metformin. May exert effects via contents of steroidal saponins Reputedly stimulates mammary growth	No data for humans. Minor abnormalities in blood and pathological specimens in rats	Abascal 2008, Bruckner 1993, Humphrey 2007, MacIntosh 2004, Rasekh 2008, Romm 2010
Fennel (*Foeniculum vulgare*) الشومر	Contains anethole, considered weakly estrogenic; may increase breast milk production or assist with the 'let-down' reflex. Reputedly stimulates mammary growth	Essential oil, may be toxic in large amounts	Abascal 2008, Bingel 1994, Bruckner 1993, Humphrey 2007, Low Dog 2009, Mills 2006, Mortel 2013, Romm 2010
Shatavari (*Asparagus racemosus*)	Estrogenic; may stimulate production by increasing prolactin. Increases weight of mammary gland in animal studies	Runny nose, itchy conjunctivitis, contact dermatitis and cough. May have laxative effect	Bingel 1994, Chaudhury 1983, Mortel 2013, Zapantis 2012

Drug Effects on Lactation

Anise or Aniseed *(Pimpinella anisum)* اليانسون	Contains anethole, considered weakly estrogenic; the aromatic compound in anise may act as a dopamine receptor antagonist	Possible allergen for some people	Abascal 2008, Bingel 1994, Bruckner 1993, Humphrey 2007, Low Dog 2009, Romm 2010
Milk thistle *(Silybum marianum)* الخرفيش	Appears to stimulate prolactin; possibly estrogenic	None known	Abascal 2008, Bingel 1994, Capasso 2009, Low Dog 2009, Mills 2006, Mortel 2013
Barley (*Hordeum vulgare*) الشعير	Polysaccharide stimulates prolactin	None known. Commonly consumed grain, also used to make beer	Bingel 1994, Humphrey 2007, Koletzko 2000, MacIntosh 2004, Sawagado 1988
Malunggay or Drumstick *(Moringa oleifera)*	Increases prolactin	None known. Commonly consumed as a vegetable in the Phillipines and elsewhere	Bingel 1994

Drugs Contraindicated during Lactation

Table 1-5. Agents Contraindicated During Lactation, Hazardous to Milk Production

Drug Class	Agents	Comments
Antiestrogens	Danazol GNRH agonists (e.g., leuprolide)	Ovarian suppression through pituitary-ovarian axis, inhibiting hormone production
	Anastrazole	Estrogen suppression through aromatase inhibition
Antiviral	Amantadine	Can suppress lactation by increasing dopamine
Dopamine agonists	Ropinirole Selegiline Rotigotine Dopamine	Lower serum prolactin concentrations, preventing lactation
Decongestants	Pseudoephedrine Propylhexedrine Phenylephrine	Oral intake can suppress milk production with single doses; topical application has a significantly lower risk unless overused
Ergots	Ergotamine Dihydroergotamine	Inhibit prolactin, preventing lactation
Ergot derivatives	Bromocriptine Cabergoline	Likely safe if treating hyperprolactinemia; otherwise contraindicated
Ethanol	Alcohol	Chronic ingestion will suppress milk production
Nicotine	Cigarettes	Decreased prolactin concentrations, reduced antioxidant properties of breast milk
Selective estrogen receptor antagonists	Tamoxifen Raloxifene	Inhibit estrogen effects in breast tissue

GNRH = gonadotropin-releasing hormone.

Drugs Contraindicated during Lactation

Table 1-6. Agents Contraindicated During Lactation, Hazardous to the Infant

Drug Class	Agents	Comments
Antiarrhythmic	Amiodarone	Several potential toxicities (e.g., pulmonary)
Anticholinergic	Dicyclomine	Contraindicated in infants < 6 months, apnea
Anti-infectives	Dapsone	Hemolytic anemia
	Rifabutin	Rash, suppression of white blood cells
	Flucytosine	Bone marrow suppression
	Foscarnet	Renal toxicity, seizures
CNS stimulants	Dextroamphetamine Amphetamines Methylphenidate	Not recommended; monitor infant for adverse events and appropriate weight gain
Cytotoxic agents	Antimetabolites, alkylating agents, etc Hydroxyurea	High potential of toxicity for the infant, including immunosuppression
Illicit substances	Cocaine, heroin, marijuana, etc.	High potential for significant toxicities in the infant

Drugs Contraindicated during Lactation

Immunosuppressants	Cyclosporine Tacrolimus	Not recommended; if used, monitor infant (for serum concentrations and adverse events)
	Everolimus Sirolimus	Not recommended until more information is available on these agents
	Mycophenolate	Not recommended, increase in infection rate
Leprostatic	Thalidomide	Several potential toxicities
Mood stabilizer	Lithium	High potential of toxicity in the infant, near therapeutic serum levels
Monoamine oxidase inhibitors	Isocarboxazid Phenelzine Selegiline Tranylcypromine	No information is available regarding these agents in breastfeeding. Other antidepressants are better options
Radioactive substances	I^{131}, etc.	Transfer of radioactive agents to the infant, destruction of thyroid tissue
Skeletal muscle relaxant	Tizanidine	Sedation, hypotension
Tetracyclines	Tetracycline Doxycycline Minocycline	Low penetration into milk, but therapy > 3 wk is not recommended due to potential of staining of teeth or changes in bone growth
Tricyclic agent	Doxepin	Significant sedation, respiratory depression
Vitamin A derivatives	Etretinate Isotretinoin	Excessive vitamin A intake and related toxicities, including liver damage and death