Mechanisms of Drug Entry into Human Milk

- The amount of drug excreted into milk depends on a number of kinetic factors:

  1) the lipid solubility of the drug,

  2) the molecular size of the drug,

  3) the blood level attained in the maternal circulation,

  4) protein binding in the maternal circulation,

  5) oral bioavailability in the infant, and the mother, and

  6) the half-life in the maternal and infant's plasma compartments.

  Using these kinetic terms, one can frequently estimate the probability that a medications will enter will.But the only true test are the research studies published in the literature.With these in hand, we can frequently estimate the absolute dosage an infant will receive from his/her mothers' milk. But remember, all patients are unique, and wide variations can exist.

Early Postpartum

- Drugs enter milk primarily by diffusion, but also by secretory methods.They pass from the maternal plasma compartment through the capillary walls into the alveolar cell lining the milk buds.They must generally pass through both walls of the alveolar cells to penetrate milk. During the first 4 to 10 days of life, large gaps between alveolar cells exist. These gaps permit enhanced access for most drugs, many immunoglobulins, maternal lymphocytes, and other maternal proteins to the milk. Soon after the first week, the alveolar cells swell, subsequently closing the intracellular gaps and limiting access to the milk.It is generally agreed, that medications penetrate milk more during the neonatal period than in mature milk, although there are exceptions.A frequently asked question is why it is safe for a pregnant woman to take a medication and it may not be safe for the breastfeeding mother. Remember, in the pregnant woman,the mothers' system takes care of metabolizing and eliminating drugs, whereas in the breastfed newborn, the infant himself must metabolize and eliminate the drug. This may be difficult for some infants, and therefore, early postpartum, a complete reassessment is required to ascertain if it is safe for a breastfeeding mother to take a specified medication.

Maternal Plasma Level:

- In most instances, the most important determinant of drug penetration into milk is the mother's plasma level. Almost without exception, as the level of the medication in the mother's plasma begins its rise, the concentration in milk begins its rise as well. Drugs both enter milk, and in most cases, exit milk as a function of the mother's

plasma level. As soon as the maternal plasma level of a medication has fallen, the milk level soon follows.Because the maternal plasma level of the medication is such a major determinant in the amount of medication transferred to milk,many drug delivery systems that deliver only exceedingly small levels to the plasma are preferred in breastfeeding mothers. These include inhaled adrenergics such as the beta-2 agonists (Ventolin), inhaled corticosteroids (Azmacort),and intranasal steroids used for allergic rhinitis (Flonase, Vancenase), or any other medication that attains poor or short lasting plasma levels.

- ## Ion Trapping:

- In some instances, drugs become ion trapped in milk, meaning that due to the lower pH of human milk, the physicochemical structure of the drug changes, and prevents its perfusion back into the maternal circulation. Trapping can also occur as due to specialized transport systems,that "pump" substances (such as iodine) into milk.This is important in weakly basic drugs (barbiturates), iodides, and maybe lithium.In these instances, the drug may concentrate in milk at high milk:plasma ratios. Because of this problem, we seldom use iodinated products in breastfeeding mothers. Such products include expectorants such as SSKI (saturated solution of potassium iodide),or even Betadyne (povidone iodide), which can be absorbed significantly from vaginal surfaces and produce high plasma iodine levels. This is another reason that I-131 used to destroy a hyperactive thyroid can produce high milk levels of radioactive iodine and damage a breastfed infants thyroid function.

- ## Protein Binding and Lipophilicity:

- Of the many factors, perhaps the two most important and useful are the degree of protein binding, and lipid solubility. Drugs that are extremely lipid soluble, penetrate milk in higher concentrations almost without exception. Of particular interest are the drugs that are active in the central nervous system (CNS).CNS active drugs invariably have unique characteristics to enter into milk.Therefore, if a drug is active in the central nervous system, somewhat higher milk levels can be expected. Protein binding also plays a very important role. Most drugs circulate in the maternal plasma bound to a large molecular weight protein called albumin. That that is not bound, remains freely soluble in the plasma.It is the "free" component that transfers into milk, while the bound fraction stays in the maternal plasma unable to reach the tissues. Therefore, drugs that have high maternal protein binding, almost invariably produce lesser levels in milk.So,when choosing between medications of the same class,always choose the medication with the greater protein binding.

- ## Oral Bioavailability:

- Once a drug has entered the mother's milk and has been ingested by the infant, it must traverse through the infant's GI tract and be absorbed.The term "Oral Bioavailabilty" refers to the amount of a drug that actually reaches the circulation of the individual.While, many drugs have poor oral absorption kinetics and are poorly absorbed into the infant's blood stream,others are destroyed in the acidic milieu of the stomach, while others are rapidly extracted by the liver and fail to ever reach the infant's circulation. Although we understand oral bioavailability in adults reasonably well, our understanding of the specifics of oral absorption in infants is somewhat rudimentary. Still, many drugs that are poorly bioavailable in adults, are similarly so in infants. Oral bioavailability is a useful tool to estimate just how much of the drug

will be absorbed by the mother or infant. In general, the infant's stomach is quite acidic and can denature many drugs. Further, some drugs are poorly absorbed when ingested with calcium rich foods and particularly milk. In addition, many drugs are sequestered in the liver and never actually reach the plasma compartment where they are active. These absorption problems tend ultimately to reduce the overall effect of many drugs.Classic illustrations of poor oral bioavailability include the aminoglycoside antibiotic Gentimycin, the third generation cephalosporins such as Rocephin, and morphine. There are certainly exceptions to this rule, and one must always be aware that the action of a drug in the GI tract can also be profound such as with the antibiotics, producing diarrhea, constipation, and sometimes syndromes such as pseudo membranous colitis with the overgrowth of the bacteria C. Difficile. Although there are many exceptions, a good rule of thumb is that far less than 1% of the maternal dose of a drug will ultimately find its way into the milk and subsequently the infant (although there are wide variations).

- ## Molecular Weight:

- In general, the lower the molecular weight of a medication,the more likely it is to penetrate into human milk,simply because diffusion through the alveolar epithelial cell is much easier. Medications with molecular weights less than 300 are considered smaller and will tend to penetrate to milk in higher concentrations than those with higher molecular weights. An example of a low molecular weight drug is ethanol (Alcohol). With a molecular weight of 120,it rapidly equilibrates between the plasma and milk compartments.Many of the amphetamines and diet medications unfortunately have low molecular weights as well. Drugs with molecular weights of 600 or greater are unlikely to penetrate milk in high concentrations.Typical examples of drugs with high molecular weights that are basically excluded from milk would include heparin(30,000), antibodies such as Remicade,and insulin(6000).

- ## pKa:

- The pKa of a drug is the pH at which the drug is equally ionic and nonionic. The more ionic a drug is, the less capable it is of transferring from the milk compartment to the maternal plasma compartment. Hence they become trapped in milk (ion-trapping).This term is useful, because drugs that have a pKa higher than 7.2 may be sequestered to a slightly higher degree than one with a lower pKa. Drugs with higher pKa generally have higher Milk:Plasma ratios.Hence, choose drugs with a lower pKa.

- ## General Rules for the Health care Consultant

- 1. Determine if the drug is absorbed from the GI tract. Many drugs such as the aminoglycosides, vancomycin, cephalosporin antibiotics (third generation),Epsom salts, and magnesium salts are so poorly absorbed that it is unlikely the infant will absorb significant quantities.At the same time, be observant for GI side effects from drug trapped in the GI compartment of the infant.

  2. Review the data on the drug. Determine if the milk:plasma ratio is high (>1). Determine if the amount absorbed by the infant has been reported to produce side effects.Review the dose that is expected to be absorbed,and compare that to the pediatric dose if known. Although useful, the milk:plasma ratio has one great weakness, and that is that it is only a ratio. It does not provide a user with

information as to the absolute amount of drug transferred to the milk. Even if the drug has a high milk:plasma ratio, if the maternal plasma level of the medication is very small (such as with propranolol), then the absolute amount of a drug entering milk will still be quite small.

3. If you are provided a choice, try to choose shorter half-life drugs, since they generally enter milk at lower levels.They also do not tend to accumulate in the infant's plasma. Be caution of drugs with "active" metabolites that may high longer half-lives. Remember,long half-life drugs may accumulate in the infant and provide problems if they are "active"

4. Be cautious of drugs that have long pediatric half-lives, as they are known to continually build up in the infant's plasma over time.The barbiturates and benzodiazepines such as Valium are classic examples.

5. If you are provided a choice, choose drugs that have higher protein binding, because they are more often sequestered in the maternal circulation and do not transfer as readily to the milk, and hence, the infant. Without doubt, the most important parameter that determines drug penetration into milk is probably protein binding. Choose drugs with high protein binding.

6. Although not always true, I have generally found that drugs that affect the brain,frequently penetrate milk in somewhat higher levels simply due to their chemistry.So if the drug in question produces sedation, depression, etc. in the mother, it is likely to penetrate the milk, with similar, although reduced, effects in the infant.Just be more caution of CNS active drugs.

7. With shorter half-life drugs, it is possible to reduce the infant's exposure to the drug by waiting for 2-3 hours or longer after dosing before feeding the infant. Remember, the milk level is directly proportional to the maternal plasma level. Determine the time-to-peak interval, as this will indicate how long the mother must wait before feeding.However, you must first determine the dosage form administered. If the tablet formulation is a prolonged release form, then all prior assumptions about half-life are worthless, and you must assume that the drug has a long half-life (12-24 hrs).

8. With radioactive compounds,and for any dangerous drug, wait 4-5 half-lives before starting breastfeeding. After 5 half-lives, approximately 98% of a drug or radioisotope is eliminated. But to be sure,just check the table put out by the Nuclear Regulatory Commission,its really accurate.

9. Remember, that anything applied to the nipple is likely to be absorbed by the infant. Be very cautious. Do not assume that topical vitamins (vitamin E) are innocuous. With most topical preparations such as hydrocortisone,if you can see the medication,you've applied too much.

10.All drugs of abuse are obviously contraindicated in breastfeeding mothers. After maternal ingestion,small amounts of drugs of abuse may transfer to the infant over the next few days, and they may reside in the neonate for long periods.Therefore, the infant may test positive for weeks to months after maternal exposure.Mothers who abuse drugs should be forewarned that their infants will test drug screen positive for 2-4 weeks or more depending on the type of drug ingested.

11.Determine the side effects most likely to occur in the infant and inform the mother and yourself of these.Mothers should be forewarned to better safeguard their infant. Many may not realize that diarrhea, constipation, sedation, or weakness, etc, may forewarn of neonatal absorption and medication problems.