

Considerations in Pregnant or Lactating Patients

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Pregnant animals are a unique population with respect to their response to xenobiotic exposures, either therapeutic or accidental. The dynamic physiologic changes that occur within the maternal-placental-fetal unit during pregnancy influence the pharmacokinetic processes of xenobiotic absorption, distribution, metabolism, and elimination. In lactating patients, the xenobiotic concentration in milk is directly proportional to the corresponding concentration in maternal plasma. For most xenobiotics, the amount ingested by neonates rarely attains toxic concentrations. However, xenobiotic toxicity can develop in the pregnant or lactating animal, fetus, or neonate when sufficient compound is present to exert a damaging effect on cells. Conversely, subtherapeutic concentrations of xenobiotics may lead to treatment failures in the pregnant or lactating animal.¹ There is a scarcity of data on specific pharmacokinetic measurements during pregnancy and lactation in dogs and even less in cats. Most specific information on pharmacokinetics presented in this chapter is based on comparative data from humans and laboratory animals (Box 17-1).

Pregnant Patients

General Considerations

In dogs, apparent serum concentrations of progesterone and estradiol are similar in pregnant and nonpregnant cycles except for the abrupt decrease of both at parturition. However, if corrections are made for the hemodilution that occurs during pregnancy, both steroid hormone concentrations are significantly higher in the last half of gestation.² This is supported by increased fecal estradiol and progesterone concentrations during the second half of pregnancy.³ Increased hepatic clearance and increased metabolism by the uterus and mammary gland also contribute to the absence of obvious increase in estradiol and progesterone concentrations during pregnancy.⁴ In addition, thyroxine and adrenocortical hormones are increased during the latter half of gestation. The combined effect of increased hormone secretion during pregnancy results in alterations in dermal, pulmonary, cardiovascular, renal, gastrointestinal, and hepatic function (Table 17-1). Although these changes are necessary for a successful pregnancy, unique absorption, distribution, metabolism, and clearance of xenobiotics must be considered when using drugs to treat or prevent disease or in response to accidental toxin exposures.

Absorption

Gastrointestinal

The site of absorption for most xenobiotics is the small intestine because of its large surface area and the fact that the oral route is a common route of administration. Xenobiotic

Box 17-1 Did You Know That Xenobiotics ...

Xenobiotics are chemical compounds (e.g., medications, other organic substances) that are found in animals but are not normally produced or expected to be present (or present at that concentration).

Table 17-1 Physiologic Changes during Pregnancy That Alter Pharmacokinetics

Physiological Parameter	Change
Absorption	
Gastric pH	Increased
Gastric emptying time	Increased
Intestinal motility	Decreased
Pulmonary function	Increased
Cardiac output	Increased
Blood flow to the skin	Increased
Absorption from IM-administered xenobiotics	Increased
Distribution	
Plasma volume	Increased
Total body water	Increased
Plasma proteins	Decreased
Body fat	Increased
Metabolism	
Hepatic metabolism	Increased or decreased*
Extrahepatic metabolism	Increased or decreased*
Intestinal wall metabolism	Increased
Excretion	
Protein binding	Decreased
Glomerular filtration rate	Increased
Renal blood flow	Increased
Pulmonary blood flow	Increased
Tidal volume	Increased

*Changes to metabolism depend upon whether the xenobiotic agent is hydrophobic (increased metabolism) or hydrophilic (decreased metabolism).

absorption across the small intestine is similar between dogs and humans, and is often faster than the rate of gastric emptying, such that gastric emptying is a rate-limiting role in xenobiotic absorption.⁵ In dogs, gastric emptying after a meal is 90 minutes.⁶ For many therapeutically useful drugs, the biological half-time is long enough to ensure that stomach emptying is not a critical parameter. However, a slower intestinal transit time can significantly increase xenobiotic absorption. High progesterone concentrations during pregnancy result in delayed gastric emptying and reduced small intestinal motility, with the net effect of orally administered compounds spending a longer time in both the stomach and small intestine.⁷ As a result of prolonged intestinal transit time, there is an increase in absorption of poorly water-soluble (hydrophobic) xenobiotics and an increase in metabolism of xenobiotics by the intestinal wall. These modifications may affect (increase or decrease) the oral absorption of a drug.^{8,9} Gastric pH is also increased during pregnancy as a result of reduced gastric acid secretion and increased gastric mucous secretion. The increase in gastric pH increases the ionization of weak acids within the stomach, which reduces their absorption.

Pulmonary

Respiratory rate is unchanged during pregnancy, but tidal volume (the amount of air per breath) and pulmonary blood flow are increased, which alters the kinetics of inhaled xenobiotics in favor of alveolar uptake and elimination by exhalation.^{10,11} Aerosol (bronchodilator com-

pounds) absorption is increased. Highly lipid-soluble anesthetic agents would be absorbed more rapidly and cleared more rapidly during pregnancy. Although the rate of anesthetic induction with volatile agents is not faster, the dose requirements for volatile anesthetic drugs (e.g., halothane, isoflurane, methoxyflurane) are reduced.¹² Volatile anesthetics also have been shown to delay intramuscular absorption of ketamine (Box 17-2).¹³

Box 17-2 Did You Know That During Pregnancy ...

During pregnancy, dose requirements for inhaled anesthetics are reduced.

Box 17-3 Did You Know That During Pregnancy ...

During pregnancy, topical administration of compounded pharmaceuticals or insecticides are more likely to result in toxicity.

Skin

In humans, substantial changes in blood flow to the skin occur during pregnancy, such that circulation to the hand increases by sixfold.¹⁴ Alterations in dermal blood flow may have a significant impact on the pharmacokinetics of transdermal xenobiotic exposure (e.g., fentanyl), although this has not been studied in pregnant domestic animals.^{15,16} Topical administration of compounded pharmaceuticals or insecticides may result in toxicity during pregnancy.^{17,18} Xenobiotic absorption following intramuscular administration is also enhanced during pregnancy because of increased tissue perfusion secondary to vasodilation (Box 17-3).

Distribution

During pregnancy, increases in body weight, total body fat, cardiac output, total body water, extracellular water, and intravascular volume can influence xenobiotic distribution (Fig. 17-1). Increases in body fat allow for a larger volume of distribution for lipophilic xenobiotics. Cardiac output increases by greater than 20% in sheep, guinea pigs, goats, and rabbits and about 40% in humans during pregnancy. However, in dogs, cardiac output increases by approximately 60% during pregnancy.^{19,20} It has been suggested that the pregnancy-associated increase in progesterone concentration leads to increased aldosterone secretion and results in increased renal fluid retention. During pregnancy in most species, the resting concentration of plasma angiotensin-2 is increased.²¹ The concentration of vasopressin is also increased relative to plasma osmolality in humans and rats.²¹ Despite an increase in blood volume, mean arterial pressure is decreased.²¹ Increased total body water results in an increased hydrophilic xenobiotic distribution.²² For example, pharmacokinetic parameters calculated from the results of the intravenous administration of lidocaine in pregnant ewes showed that the volume of distribution was increased, resulting in an increase in half-life.²³ Beginning in midgestation and lasting 1 to 2 months after parturition, hemodilution occurs as reflected in a decrease in hematocrit and plasma albumin concentration.² In humans, the size of the fetus and number of fetuses influence the increase in plasma volume, but this relationship has not been studied in domestic animals.²⁴ As a result of this pregnancy-associated dilutional hypoalbuminemia, there is a decrease in total plasma concentration of a protein-bound xenobiotic substances. In addition, steroid and placental hormones and serum lipids (from increased body fat) will displace xenobiotics from protein-binding sites, resulting in a rise in free (active) xenobiotic concentration of agents that would normally be protein-bound and potentially result in an increased physiological (toxic) effect. This is most noticeable for acidic xenobiotics that are highly protein-bound.

Almost all xenobiotics cross the placenta and reach pharmacologic concentrations in the fetus after exposure of the mother. Drugs administered to the mother may cross the placenta by passive diffusion, facilitated transport, and active transport. Lipophilic, nonionized molecules less than 500 Da can cross the placenta by passive diffusion.^{25,26} In women undergoing elective cesarean sections, rapid placental transfer of ketamine,²⁷ propofol,²⁸ diazepam,^{29,30} and atropine³¹ occur such that fetal cord vein concentrations are several times higher than maternal. To date, these pharmacokinetic studies have not been done

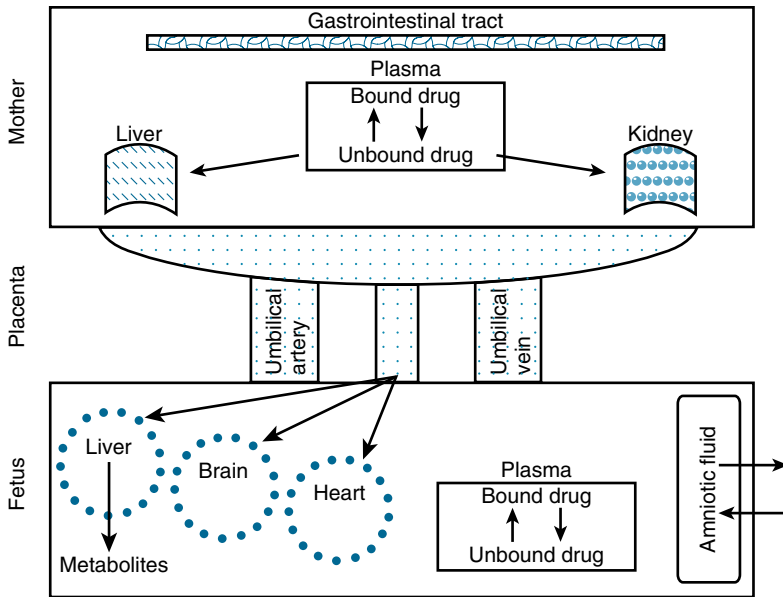


Figure 17-1 Xenobiotic distribution in the maternal-placental-fetal system. Factors affecting the pharmacokinetics and xenobiotic effects on mother and fetus are (1) altered maternal absorption; (2) increased maternal unbound xenobiotic fraction; (3) increased maternal plasma volume; (4) altered hepatic clearance; (5) increased maternal renal blood flow and glomerular filtration rate; (6) placental transfer; (7) placental metabolism; (8) placental blood flow; (9) maternal-fetal blood pH; (10) preferential fetal circulation to the heart and brain; (11) undeveloped fetal blood-brain barrier; (12) immature fetal liver enzyme activity; and (13) increased fetal unbound xenobiotic fraction.

in domestic animals but inferences have been made based on the use of these anesthetics and neonatal survival in dogs. Alpha-2 agonists (e.g., xylazine, metdetomidine), ketamine, thiobarbiturates (e.g., thiopental, thiamylal) and methoxyflurane should be avoided.^{32,33} The current recommended anesthetic protocol for canine and feline patients undergoing cesarean sections is hydromorphone or fentanyl premedication, propofol induction and inhalant anesthetic maintenance.³⁴ If premedicating with an anticholinergic, glycopyrrolate has limited placental passage compared with atropine with significantly lower maximum fetal to maternal serum concentration (0.04-1, respectively).³⁵

Maternal and fetal blood pH and plasma protein binding also influence the rate of passive diffusion across the placenta. The fetal plasma pH is slightly more acidic than the maternal. Consequently, xenobiotics that are weak bases are nonionized and able to easily penetrate the placental barrier. However, after crossing the placenta and making contact with the relatively acidic fetal blood, these molecules become more ionized, leading to “ion trapping.” Protein-bound xenobiotics do not cross the placenta. In general, fetal plasma proteins bind xenobiotics with less affinity compared with those of the dam (e.g., ampicillin), with the exception of a few xenobiotics (e.g., salicylates) that have a greater affinity for fetal plasma proteins than maternal. Compounds that become bound to fetal proteins represent a depot of xenobiotic exposure in the fetus that would prolong fetal exposure after cessation of maternal exposure. Although hydrophilic compounds cannot cross the placenta by passive diffusion, they cross via aqueous diffusion through the water-filled pores between the cells (paracellular pathway) (Box 17-4).²⁵

Box 17-4 Did You Know That During Pregnancy ...

During pregnancy, almost all xenobiotics reach pharmacologic concentrations in the fetus after exposure of the mother and umbilical vein concentrations are typically several times higher than maternal.

Metabolism

Alterations in the hormonal milieu of pregnancy are associated with changes in xenobiotic metabolism. In most cases, xenobiotic metabolism occurs primarily in the liver. Decreased protein binding during pregnancy results in greater xenobiotic availability for hepatic biotransformation, a process that renders a xenobiotic more water soluble and thus readily excreted by the kidneys. Hepatic metabolism during pregnancy has been well investigated in rats and to a much lesser extent in domestic animals. Changes in xenobiotic metabolism may have an impact on the first-pass effect of drugs given orally during pregnancy. Some microsomal enzymes of the hepatic cytochrome P-450 system are induced by progesterone, resulting in a higher rate of xenobiotic metabolism by the liver.³⁶ For example, it has been found clinically that the phenytoin dosage needs to be increased during pregnancy to maintain plasma concentrations that are adequate to control epileptic seizures in women.³⁷ However, the capacity for hepatic biotransformation is six times greater in dogs compared with humans.³⁸ Some microsomal enzymes are competitively inhibited by progesterone and estradiol, resulting in impaired xenobiotic metabolism.³⁹ Because of hormonal inhibition of hepatic microsomal oxidases, theophylline degradation is delayed during pregnancy.⁴⁰ Elevated progesterone during pregnancy also inhibits hepatic glucuronidation and extrahepatic cholinesterase activity.⁴¹ However, in a pharmacokinetic study involving dogs treated with lamotrigine during and after pregnancy, the authors concluded that pregnancy has little or no effect on glucuronidation.⁴²

Pregnancy may enhance a drug's biotransformation by increasing the access of the drug to the site of metabolism (e.g., liver) and by increasing the activity of the enzymatic system (e.g., hepatic cytochrome P-450 family).¹ However, during pregnancy, there may be decreased expression of genes encoding for hepatic cytochrome P-450.^{43,44} Most biotransformation reactions present in the liver have also been described within the placenta, although placental biotransformation capacity is many times less than that of the liver.⁴⁵ The placenta contains several enzymes that are capable of metabolizing xenobiotics via oxidation, reduction, hydrolysis, and conjugation pathways. For example, the placental cytochrome P-450 enzyme 1A1 is induced following exposure to aromatic hydrocarbons found in tobacco smoke.⁴⁶ Alternatively, toxic intermediate formation may result from the placental oxidative biotransformation system. Xenobiotics that are not metabolized by the placenta enter the fetal hepatic circulation via the umbilical vein. However, approximately 50% of umbilical venous blood flow will bypass the liver via the ductus venosus, contributing to a possible accumulation of xenobiotics within the fetus. The near-term dog fetus shows evidence of a functioning enterohepatic circulation of bile salt, and xenobiotics can be found in meconium. Because of the small bile salt pool, apparent limited capacity of the gallbladder to concentrate bile, and evidence of a functional hepatic bypass, fetal hepatic metabolism is immature compared with that of the adult.⁴⁷

Elimination

As a general rule, lipophilic compounds will be cleared mainly by metabolism, whereas hydrophilic compounds will be subjected to renal and/or biliary clearance. Xenobiotic clearance from plasma is generally faster in dogs than in humans (lidocaine: 14 vs 30 mL/minute per kg;^{48,49} metoclopramide: 8 vs 25 mL/minute per kg;⁵⁰ domperidone: 10 vs 20 mL/minute per kg;⁵¹ and pentobarbital: 1 vs 2 mL/minute per kg^{52,53}). In dogs, renal blood flow and glomerular filtration rate are increased during pregnancy.^{54,55} In humans, renal blood flow is increased by 60% to 80% and glomerular filtration is increased by 50% during

Box 17-5

Did You Know That During Pregnancy ...

During pregnancy, the amount of ampicillin necessary to maintain antimicrobial drug concentrations doubles and the elimination half-life for cephalosporins is reduced.

pregnancy.⁵⁶ Decreased protein binding during pregnancy results in more unbound xenobiotics available for renal excretion. As a result of increased glomerular filtration rate, the rate of elimination for compounds cleared by the kidney is enhanced (e.g., resulting in a reduced half-life), which can have a significant impact on drug treatment. For example, the amount of ampicillin necessary to maintain antimicrobial drug concentration doubles during pregnancy because of the combined effect of increased volume of distribution and rate of elimination.⁵⁷ The elimination half-lives are also reduced for cephalosporin and some anticonvulsants. Opposite results were described for gentamicin because increased clearance and decreased half-life occur in women^{58,59} and ewes⁶⁰ during pregnancy but did not change for mares.⁶¹ The fetus relies largely on the maternal system for elimination of xenobiotics. Elimination from the fetus to the mother via the placenta is by diffusion. However, because most xenobiotic metabolites are polar and not capable of simple diffusion, they can accumulate within the fetal compartment. Placental efflux transporters (e.g., P-glycoprotein) actively remove xenobiotics from the fetal circulation into the maternal circulation for elimination (Box 17-5).^{38,62-65}

Lactating Patients

General Considerations

During lactation, estrogen and progesterone concentrations are at baseline, whereas prolactin concentrations are elevated. Milk is produced in mammary alveolar cells from which it is expelled by contractile myoepithelial cells into the duct system. Prolactin stimulates the synthesis of milk proteins such as α -lactalbumin. Milk proteins are synthesized within ribosomes in the rough endoplasmic reticulum and transported to the Golgi region of the mammary alveolar cells, where the protein is packaged into vacuoles. The milk protein vacuoles are pinched off and fuse with the alveolar cell membrane to become released into the alveolar lumen. The major proteins found in the milk are casein, lactoferrin, α -lactalbumin, and IgA. α -Lactalbumin, along with galactosyltransferase, uridine diphosphogalactose, and glucose form lactose.⁶⁶ Lactose is the principal osmotically active compound in milk. Although water is the principal component of milk, the amount of water within milk is regulated by the quantity of lactose. A reciprocal relationship among lactose and sodium, potassium, and chloride concentrations is maintained to keep the total osmolality of milk similar to that of blood.⁶⁷ Fat is delivered to mammary tissue from serum chylomicra of gastrointestinal origin and from endogenous low-density lipoproteins. Triglycerides are hydrolyzed at the capillary level, whereupon glycerol and free fatty acids enter the mammary alveolar cells by passive diffusion. Unlike plasma, canid milk contains on average 9.5% of emulsified fat.⁶⁸ Milk fat can concentrate lipid-soluble xenobiotics, causing the total amount of xenobiotic in milk to increase. For highly lipid-soluble drugs (e.g., diazepam and chlorpromazine), well more than half of the total amount of drug in milk is found in milk fat.⁶⁹

Xenobiotics enter and exit the alveolar lumen by passive diffusion through the lipid portion of the alveolar membrane or via active transport through protein channels in the membrane. Passive diffusion is the most common route in which xenobiotics enter milk. Xenobiotics pass through the mammary epithelium by passive diffusion down a concentration gradient on each side of the membrane. With passive diffusion, the xenobiotic concentration in milk is directly proportional to the corresponding xenobiotic concentration in maternal plasma. The higher the dose administered to the mother, the more xenobiotic that will pass into the milk. Milk concentrations are the highest following intravenous administration compared with other routes of administration.

Box 17-6 Did You Know That During Lactation ...

During lactation, milk concentrations of xenobiotics are the highest following intravenous administration compared with other routes of administration.

Box 17-7 Did You Know That During Lactation ...

During lactation, xenobiotics that are weak bases (e.g., erythromycin and antihistamines) are more likely to pass into milk than weak acids (e.g., barbiturates and penicillins).

Table 17-2 Milk to Plasma (M:P) Ratios Relating to the Ratio between the Area Under the Curve of the Drug in Women

Drug	M:P Ratio
Amoxicillin ⁷⁴	0.014-0.043
Penicillin ⁷⁵	0.02-0.2
Prednisolone ⁷⁶	0.078-0.221
Diazepam ⁷⁷	0.08-0.13
Cephalothin ⁷⁴	0.14
Metronidazole ⁷⁸	1.7
Fentanyl ⁷⁹	2.45
Morphine ⁸⁰	2.46
Acyclovir ⁸¹	2.94

For those drugs excreted in milk, lactation can markedly increase drug clearance.⁷⁰ The physicochemical characteristics of the xenobiotic (i.e., molecular size, plasma protein binding, lipophilicity, and ionization) also determine how much of the compound will be transferred into milk. The mammary epithelium membrane acts as a semipermeable lipid barrier. Small pores permit xenobiotics with a low molecular weight (<200 kDa) to pass through the alveolar membrane. Larger xenobiotic molecules must dissolve in the outer lipid membrane of the epithelial cells, diffuse across the aqueous interior of the cells, dissolve in and pass through the opposite cell membrane, and then pass into the milk. Only unbound xenobiotics

in maternal plasma can diffuse across the alveolar membrane and accumulate in milk. High plasma protein binding decreases the amount of xenobiotic excreted into milk, whereas high milk protein-binding results in the sustained presence of a xenobiotic in milk. Casein is the major xenobiotic-binding protein found in milk.⁷¹ However, as a general rule, milk proteins do not bind xenobiotics well.⁷² As milk (pH 7.2) is slightly more acidic than plasma (pH 7.4), compounds that are weak bases (e.g., erythromycin and antihistamines) are more likely to pass into milk than weak acids (e.g., barbiturates and penicillins). The degree of xenobiotic ionization, determined by the xenobiotic pKa (ionization constant) and the pH of the plasma and the milk, plays a role in determining the amount of xenobiotic excreted in the milk in a process called “ion or xenobiotic trapping,” similar to the fetal circulation. A good example of ion trapping can be seen with orbifloxacin because, like other fluoroquinolones, it is amphoteric with its carboxylic acid group and basic amine functional group and it extensively passes from blood into milk (Boxes 17-6 and 17-7).⁷³

Although water-soluble xenobiotics must cross through pores within the alveolar membrane, lipid-soluble xenobiotics dissolve into the lipid bilayer of the alveolar membrane. The more lipid-soluble the xenobiotic, the greater the quantity and the faster the transfer into milk. Another factor that comes into play is the retrograde diffusion of xenobiotics from the milk back into maternal plasma. Studies in cattle indicate that compounds instilled directly into the udder pass out of the milk and are detectable in the plasma. The milk-to-plasma ratio (M:P) compares milk with maternal plasma xenobiotic concentrations and serves as an index of the extent of xenobiotic passage into milk to estimate a neonate’s exposure to xenobiotics through milk (Table 17-2). The milk xenobiotic concentration usually does not exceed the maternal plasma concentration but even when M:P is greater than 1, the amount of xenobiotic ingested by a neonate is rarely sufficient to attain therapeutic or toxic

concentrations. Peak drug concentrations after oral administration occur 1 to 3 hours after the dose.

Analgesics and Anesthetics

Ibuprofen, naproxen, and diclofenac do not cross into milk (M:P = 0.01).⁸² However, the former two are known to cause toxicity in dogs and should therefore be avoided in both lactating and nonlactating canids. On the other hand, aspirin crosses into breast milk (M:P = 0.3) and is slower to be eliminated from milk than the plasma. A cumulative effect from aspirin could have adverse consequences on suckling neonates. In addition, the elimination half-life of aspirin is considerably longer in neonates than mature animals, which increases the likelihood of drug accumulation and adverse effects. As a general rule, nonsteroidal antiinflammatory drugs should be avoided during lactation.⁸³

Meperidine (pethidine) also crosses into breast milk (M:P ~1). The half-life of pethidine (13 hours) and its hepatic metabolite, norpethidine (63 hours), in the neonate can lead to high neonatal plasma concentrations over time. Neonates nursing from mothers who were treated with intravenous pethidine following a cesarean section were neurologically and behaviorally depressed.⁸⁴ Dipyrone and its metabolites are passed into milk and have resulted in cyanosis in a human nursing neonate.⁸⁵ Benzodiazepines with long-acting metabolites can accumulate in infants, especially neonates, because of their immature excretory mechanisms and have caused adverse effects in infants.⁸⁶ Milk halothane concentrations equal or surpass concentrations in maternally inhaled air.⁸⁷

Antibiotics

Penicillins appear in milk in amounts that could lead to disruption of neonatal gastrointestinal flora. Similar to penicillins, cephalosporins could lead to disruption of neonatal gastrointestinal flora.⁷⁴ First- and second-generation cephalosporins are considered to be safer in neonates compared with third-generation agents because of their activity against normal flora.

Following oral administration, clavulanic acid is transferred into the milk but no harmful effects have been reported.⁸⁸ Sulfamethoxazole is secreted into milk and has a long elimination half-life in neonates (36 hours for human neonates).

Xenobiotics Affecting Lactation

In addition to the effects of xenobiotics on the neonate, the potential effects of xenobiotics on lactation should be considered. Many xenobiotics affect prolactin secretion centrally. Cyproheptadine, bromocriptine, cabergoline, and metergoline lower maternal plasma prolactin concentrations and should be avoided unless cessation of lactation is desired. Sympathomimetics can also decrease milk production, probably by centrally decreasing suckling-induced oxytocin and prolactin release and peripherally reducing mammary blood flow.⁸⁹ Metoclopramide, a dopamine agonist, is used to stimulate lactation and is concentrated in milk because of ion trapping. Neonatal plasma prolactin concentrations may be elevated after maternal administration of metoclopramide.⁹⁰ Like oxytocin, prostaglandin $F_{2\alpha}$ administered intranasally increases milk ejection.⁹¹ Fenugreek is an herbal product used in human medicine⁹²⁻⁹⁴ and has been shown to have oxytocin-like activity in animals.⁹⁵ Although the use of herbal products seems to be increasing because they are viewed as safer or more natural alternatives to pharmaceutical products, the potential exists for herbal products to have all of the properties of pharmaceuticals, ranging from clinical usefulness to toxicity.

Conclusion

Although the majority of pregnant or lactating patients are healthy and drug administration can be avoided, acute disorders such as infection may require short-term medical treatment. The results of one veterinary survey indicate that the possibility of pregnancy was rarely considered when prescribing medications to companion animals.⁹⁶ Within

veterinary medicine, pharmacokinetic data are typically generated in small groups of normal healthy animals, and it is often assumed that these data will reflect the drug's kinetic properties across the intended patient population. Few pharmacokinetic studies of drug absorption, metabolism, distribution, and elimination during pregnancy or lactation exist specifically for canids and felids. Information to modify dose schedules to ensure efficacy and minimize the risk of toxicity is definitely necessary. Whenever drugs are used in pregnant and lactating patients, the prescribing clinician must explain the relative benefits and risks associated with the treatment and obtain informed consent from the owner.

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