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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 physiological 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. 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 review is based on comparative data from humans and laboratory animals.

PREGNANT PATIENTS

In dogs, apparent serum concentrations of progesterone and estradiol are similar in pregnant and nonpregnant cycles except for the abrupt decrease in both at parturition. However, if corrections are made for hemodilution that occurs during pregnancy, both steroid hormone concentrations are significantly higher in the last half of gestation.[1] This is supported by increased fecal estradiol and progesterone concentrations during the second half of pregnancy.[2] 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.[3] In addition, thyroxine and adrenocortical hormones are increased during the latter half of gestation. The combined effects

...ased hormone secretion during pregnancy results in alterations in ...nal, pulmonary, cardiovascular, renal, gastrointestinal, and hepatic ...ion (Table 12-1). Although these changes are necessary for a successful ...regnancy, unique absorption, distribution, metabolism, and clearance ...enobiotics must be considered when using drugs to treat or prevent ...ase or in response to accidental toxin exposures.

...SORPTION

...astrointestinal

...e site of absorption for most xenobiotics is the small intestine due to its ...e surface area. Xenobiotic absorption across the small intestine is similar between dogs and man, and is often faster than the rate of gastric ...ptying, such that gastric emptying is a rate-limiting role in xenobiotic ...orption.[4] In dogs, gastric emptying after a meal is 90 minutes. For ...ny therapeutically useful drugs, the biological half-time is long enough ...ensure that stomach emptying is not a critical parameter. However, a

...ble 12–1
...ysiologic Changes During Pregnancy That ...fer Pharmacokinetics

...ysiological Parameter	Change
...bsorption	
...astric emptying time	Increased
...testinal motility	Decreased
...ulmonary function	Increased
...ardiac output	Increased
...ood flow to the skin	Increased
...stribution	
...asma volume	Increased
...otal body water	Increased
...asma proteins	Decreased
...ody fat	Increased
...etabolism	
...epatic metabolism	Increased or Decreased
...trahepatic metabolism	Increased or Decreased
...cretion	
...nal blood flow	Increased
...omerular filtration rate	Increased
...ulmonary function	Increased

slower intestinal transit time can significantly increase xenobiotic absor
Increased progesterone concentrations during pregnancy result in de
gastric emptying and reduced small intestinal motility, with the net
of orally administered compounds spending a longer time in bot
stomach and small intestine.[6] As a result of prolonged intestinal t
time, there is an increase in absorption of poorly water-soluble xenob
and an increase in metabolism of xenobiotics by the intestinal
Gastric pH is also increased during pregnancy as a result of reduced
tric acid secretion and increased gastric mucus secretion. The increa
gastric pH increases the ionization of weak acids within the stom
which reduces their absorption.

Pulmonary

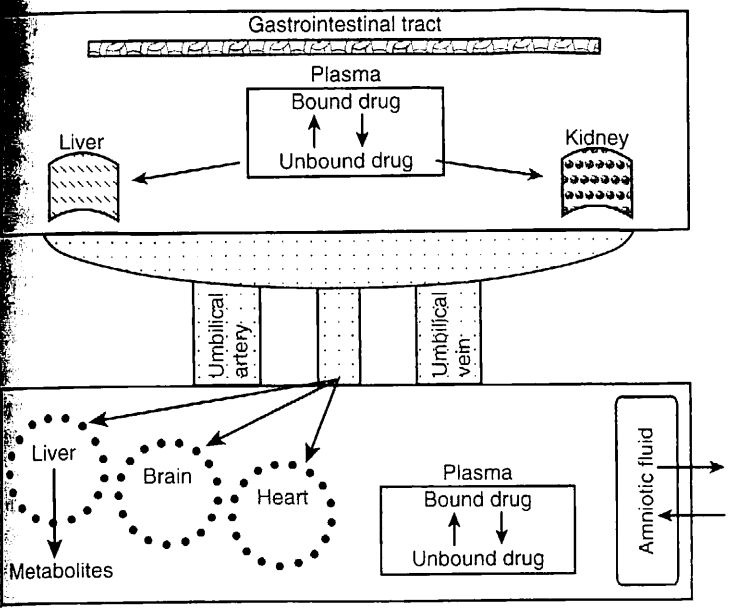
Respiratory rate is unchanged during pregnancy but tidal vol
(the amount of air per breath) and pulmonary blood flow are increa
which alters the kinetics of inhaled xenobiotics in favor of alveolar up
and elimination by exhalation.[7,8] Highly lipid-soluble anesthetic ag
would be absorbed more rapidly and cleared more rapidly dur
pregnancy. While the rate of anesthetic induction with volatile agent
not faster, the dose requirements for volatile anesthetic drugs (
halothane, isoflurane, methoxyflurane) are reduced.[9] The absorption
drugs that are administered as aerosols (bronchodilator compounds) is
increased.

Skin

In humans, substantial changes in blood flow to the skin occur dur
pregnancy, such that circulation to the hand increases by sixfold
Alterations in dermal blood flow may have a significant impact on
pharmacokinetics of transdermal xenobiotic exposure. Topical admin
tration of insecticides or compounded pharmaceuticals may result
toxicity during pregnancy. Xenobiotic absorption from intramuscu
delivery is also enhanced during pregnancy because of increased tiss
perfusion secondary to vasodilation.

DISTRIBUTION

During pregnancy, increases in body weight, total body fat, total bo
water, extracellular water, intravascular volume, and cardiac output c



re 12–1. Xenobiotic distribution in the maternal-placental-fetal system. ors affecting the pharmacokinetics and xenobiotic effects on mother and fetus 1, altered maternal absorption; 2, increased maternal unbound xenobiotic ion; 3, increased maternal plasma volume; 4, altered hepatic clearance; creased maternal renal blood flow and glomerular filtration rate; 6, placental sfer; 7, placental metabolism; 8, placental blood flow; 9, maternal-fetal blood 10, preferential fetal circulation to the heart and brain; 11, undeveloped fetal od-brain barrier; 12, immature fetal liver enzyme activity; and 13, increased l unbound xenobiotic fraction.

uence xenobiotic distribution (Fig. 12-1). The increase in cardiac ut during pregnancy in cats and dogs has not been published. wever, cardiac output increases by greater than 20% in sheep, guinea , goats, and rabbits and about 40% in humans during pregnancy. reases in body fat allow for a larger volume of distribution for lipophilic obiotics. It has been suggested that the pregnancy-associated increase progesterone concentration leads to increased aldosterone secretion d results in increased renal fluid retention. Increased total body water ults in an increased hydrophilic xenobiotic distribution. For example, rmacokinetic parameters calculated from the results of the intra- ous administration of lidocaine in pregnant ewes showed that the ime of distribution was increased, resulting in an increase in half-life.[11] ginning in midgestation and lasting 1 to 2 months after parturition,

hemodilution occurs as reflected in a decrease in hematocrit and pla albumin concentration.[1] In humans, the size of the fetus and numbe fetuses influence the increase in plasma volume, but this relationship has been studied in domestic animals.[12] As a result of this pregnancy-associa dilutional hypoalbuminemia, total plasma concentration of a prot bound xenobiotic decreases. In addition, steroid and placental hormo and serum lipids (from increased body fat) will displace xenobiotics fr protein-binding sites, resulting in a rise in free (active) xenobiotic conc tration of agents that would normally be protein-bound and potentia result in an increased physiological effect. This is most noticeable f 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 admini tered to the mother may cross the placenta by passive diffusion, facilitat transport, and active transport. Lipophilic, nonionized molecules less tha 600 Da can cross the placenta by passive diffusion.[13] In women under ing elective C-sections, rapid placental transfer of ketamine,[14] propofol, diazepam,[16,17] and atropine[18] occur such that fetal cord vein concentra tions are several times higher than maternal. Maternal and fetal blood p and plasma protein binding also influence the rate of passive diffusio across the placenta. The fetal plasma pH is slightly more acidic than th maternal. Consequently, xenobiotics that are weak bases are nonioniz and able to easily penetrate the placental barrier. However, after crossi the placenta and making contact with the relatively acidic fetal blood these molecules will become more ionized, leading to "ion trapping Protein-bound xenobiotics do not cross the placenta. In general, fe plasma proteins bind xenobiotics with less affinity compared with tho 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 tha maternal. Compounds that become bound to fetal proteins represent depot of xenobiotic in the fetus that would prolong fetal exposure aft cessation of maternal exposure. While hydrophilic compounds cann cross the placenta by passive diffusion, they cross via aqueous diffusio through the water-filled pores between the cells (paracellular pathway).

METABOLISM

Alterations in the hormonal milieu of pregnancy are associated wi changes in xenobiotic metabolism. In most cases, xenobiotic metaboli occurs primarily in the liver. Decreased protein binding during pregna results in greater xenobiotic availability for hepatic biotransformati

ocess that renders a xenobiotic more water-soluble and thus readily eted by the kidneys. Hepatic metabolism during pregnancy has been investigated in rats and to a much lesser extent in other species. nges in xenobiotic metabolism may have an impact on first-pass effect rugs given orally during pregnancy. Some microsomal enzymes of the atic cytochrome P450 system are induced by progesterone, resulting higher rate of xenobiotic metabolism.[19] For example, it has been nd clinically that the phenytoin dosage needs to be increased during gnancy to maintain plasma concentrations that are adequate to control ileptic seizures in women.[20] However, the capacity for hepatic biotrans- rmation is six times greater in dogs compared with man.[21] Some micro- mal enzymes are competitively inhibited by progesterone and estradiol, sulting in impaired xenobiotic metabolism.[22] Because of hormonal hibition of hepatic microsomal oxidases, theophylline degradation is layed during pregnancy.[23] Elevated progesterone during pregnancy also hibits hepatic glucoronidation and extrahepatic cholinesterase activity.[24] Most biotransformation reactions present in the liver have also been scribed within the placenta, although placental biotransformation pacity is many times less than that of the liver.[25] The placenta contains veral enzymes that are capable of metabolizing xenobiotics via oxida- on, reduction, hydrolysis, and conjugation pathways. For example, the lacental cytochrome P450 enzyme 1A1 is induced following exposure to romatic hydrocarbons found in tobacco smoke.[26] Alternatively, toxic ntermediate formation may result from the placental oxidative biotrans- rmation system. Xenobiotics that are not metabolized by the placenta ter the fetal hepatic circulation via the umbilical vein. However, approxi- ately 50% of umbilical venous blood flow will bypass the liver via the ctus venosus, contributing to a possible accumulation of xenobiotics thin the fetus. The near-term dog fetus shows evidence of a functioning terohepatic circulation of bile salt, and xenobiotics can be found in meco- um. Because of the small bile salt pool, apparent limited capacity of the llbladder to concentrate bile, and evidence of a functional hepatic bypass, tal hepatic metabolism is immature compared with that of the adult.[27]

LIMINATION

a general rule, lipophilic compounds will be cleared mainly by metab- sm, whereas hydrophilic compounds will be subjected to renal and/or liary clearance. Xenobiotic clearance from plasma is generally faster in gs than in man (lidocaine: 14 vs. 30 mL/min/kg[28]; metoclopramide: vs. 25 mL/min/kg[29]; domperidone: 10 vs. 20 mL/min/kg[30]; and

pentobarbital: 1 vs. 2 mL/min/kg[32,33]). In dogs, renal blood flow
glomerular filtration rate are increased during pregnancy.[34,35] In hu
renal blood flow is increased by 60% to 80% and glomerular filtrati
increased by 50% during pregnancy.[36] Decreased protein binding d
pregnancy results in more unbound xenobiotics available for renal e
tion. As a result of increased glomerular filtration rate, the rate of e
nation for compounds cleared by the kidney is enhanced, which can
a significant impact on drug treatment. For example, the amount of a
cillin necessary to maintain antimicrobial drug concentration dou
during pregnancy because of the combined effect of increased volum
distribution and rate of elimination.[37] The elimination half-lives are
reduced for cephalosporin and some anticonvulsants. The fetus r
largely on the maternal system for elimination of xenobiotics. Elimina
from the fetus to the mother via the placenta is by diffusion. Howev
most xenobiotic metabolites are polar and not capable of simple diffus
they can accumulate within the fetal compartment. Placental efflux tr
porters (e.g., P-glycoprotein) actively remove xenobiotics from the f
circulation into the maternal circulation for elimination.[21]

MILK PRODUCTION

During lactation, estrogen and progesterone concentrations are at base
while prolactin concentrations are elevated. Milk is produced in mamm
alveolar cells from which it is expelled by contractile myoepithelial c
into the duct system. Prolactin stimulates the synthesis of milk prot
such as α-lactalbumin. Milk proteins are synthesized within ribosome
the rough endoplasmic reticulum and transported to the Golgi regio
the mammary alveolar cells, where the protein is packaged into vacu
The milk protein vacuoles are pinched off and fuse with the alve
cell membrane to become released into the alveolar lumen. The ma
proteins found in the milk are casein, lactoferrin, α-lactalbumin, and
α-Lactalbumin, along with galactosyltransferase, uridine diphosphoga
tose and glucose form lactose.[38] Lactose is the principal osmotically ac
compound in milk. While water is the principal component of milk,
amount of water within milk is regulated by the quantity of lact
A reciprocal relationship between lactose and sodium, potassium, a
chloride concentrations is maintained to keep the total osmolality
milk similar to that of blood.[39] Fat is delivered to mammary tissue f
serum chylomicra of gastrointestinal origin and from endogenous l
density lipoproteins. Triglycerides are hydrolyzed at the capillary le
whereupon glycerol and free fatty acids enter the mammary alveolar c

ssive diffusion. Unlike plasma, canid milk contains on average 9.5%
mulsified fat.[40] Milk fat can concentrate lipid-soluble xenobiotics,
ng the total amount of xenobiotic in milk to increase. For highly
soluble drugs (e.g., diazepam and chlorpromazine), well more than
f the total amount of drug in milk is found in milk fat.[41]
enobiotics enter and exit the alveolar lumen by passive diffusion
ugh the lipid portion of the alveolar membrane or via active transport
ugh protein channels in the membrane. Passive diffusion is the most
mon route in which xenobiotics enter milk. Xenobiotics pass through
mammary epithelium by passive diffusion down a concentration
dient on each side of the membrane. With passive diffusion, the xeno-
ic concentration in milk is directly proportional to the corresponding
obiotic concentration in maternal plasma. The higher the dose admin-
ed to the mother, the more xenobiotic that will pass into the milk. Milk
centrations are the highest following intravenous administration
pared with other routes of administration. The physicochemical char-
teristics of the xenobiotic (i.e., molecular size, plasma protein binding,
philicity, and ionization) also determine how much of the compound
be transferred into milk. The mammary epithelium membrane acts as
emipermeable lipid barrier. Small pores permit xenobiotics with a low
lecular weight (<200 kDa) to pass through the alveolar membrane.
ger xenobiotic molecules must dissolve in the outer lipid membrane of
epithelial cells, diffuse across the aqueous interior of the cells, dissolve
nd pass through the opposite cell membrane, and then pass into the
k. Only unbound xenobiotics in maternal plasma can diffuse across the
olar membrane and accumulate in milk. High plasma protein binding
reases the amount of xenobiotic excreted into milk, whereas high milk
otein-binding results in sustained presence of a xenobiotic in milk.
sein is the major xenobiotic-binding protein found in milk.[42] However,
general rule, milk proteins do not bind xenobiotics well.[43] As milk
7.2) is slightly more acidic than plasma (pH 7.4), compounds that are
ak bases (e.g., erythromycin and antihistamines) are more likely to pass
milk than weak acids (e.g., barbiturates and penicillins). The degree
xenobiotic ionization, determined by the xenobiotic pKa (ionization
stant) and the pH of the plasma and the milk, plays a role in determin-
the amount of xenobiotic excreted in the milk in a process called
or xenobiotic trapping," similar to the fetal circulation.
While water-soluble xenobiotics must cross through pores within the
olar membrane, lipid-soluble xenobiotics dissolve into the lipid bilayer
he alveolar membrane. The more lipid soluble the xenobiotic, the
ter the quantity and the faster the transfer into milk. Another factor
comes into play is the retrograde diffusion of xenobiotics from the

Table 12–2
Milk to Plasma (M:P) Ratios Relating to the Ratio Between the Area Under the Curve of the Drug in Milk and Maternal Drug in Women

Drug	M:P Ratio
Acyclovir[44]	2.94
Amoxicillin[45]	0.014-0.043
Cephalothin[45]	0.14
Diazepam[46]	0.08-0.13
Fentanyl[47]	2.45
Metronidazole[48]	1.7
Morphine[49]	2.46
Penicillin[50]	0.02-0.2
Prednisolone[51]	0.078-0.221

milk back into maternal plasma. Studies in cattle indicate that compou instilled directly into the udder pass out of the milk and are detectable the plasma. The milk-to-plasma ratio (M:P) compares milk with mater plasma xenobiotic concentrations and serves as an index of the extent xenobiotic passage into milk to estimate a neonate's exposure to xeno otics through milk (Table 12-2). The milk xenobiotic concentration usual does not exceed the maternal plasma concentration but even wh M:P >1, the amount of xenobiotic ingested by a neonate is rarely sufficie to attain therapeutic or toxic concentrations. Peak drug concentratio following 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) However, the former two are known to cause toxicity in dogs and shou therefore be avoided in both lactating and nonlactating canids. On t other hand, aspirin crosses into breast milk (M:P = 0.3) and is slower be eliminated from milk than the plasma. A cumulative effect from t aspirin could have adverse consequences on suckling neonates. In add tion, the elimination half-life of aspirin is considerably longer in neona than mature animals, which increases the likelihood of drug accumulati and adverse effects. Meperidine (pethidine) also crosses into breast mi (M:P ~ 1). The half-life of pethidine (13 hours) and its hepatic metaboli norpethidine (63 hours), in the neonate can lead to high neonatal plasm concentrations over time. Neonates nursing from mothers who were treat with intravenous pethidine following a C-section were neurologically a

iorally depressed.[53] Dipyrone and its metabolites are passed into and have resulted in cyanosis in a human nursing neonate.[54] zodiazepines with long-acting metabolites can accumulate in infants, cially neonates, because of their immature excretory mechanisms and caused adverse effects in infants.[55] Milk halothane concentrations l or surpass concentrations in maternally inhaled air.[56]

TIBIOTICS

icillins appear in milk in amounts that could lead to disruption neonatal gastrointestinal flora. Similar to penicillins, cephalosporins d lead to disruption of neonatal gastrointestinal flora.[45] First- and nd-generation cephalosporins are considered to be safer on neonates npared with third-generation agents because of their activity against mal flora.

Following oral administration, clavulanic acid is transferred into the k but no harmful effects have been reported.[57] Sulfamethoxazole is reted into milk and has a long elimination half-life in neonates (36 hours human neonates).

ENOBIOTICS AFFECTING LACTATION

addition to the effects of xenobiotics on the neonate, the potential ects of xenobiotics on lactation should be considered. Many xenobi- ics affect prolactin secretion centrally. Cyproheptadine, bromocriptine, bergoline, and metergoline lower maternal plasma prolactin concentra- ns and should be avoided unless cessation of lactation is desired. mpathomimetics can also decrease milk production, probably by trally decreasing suckling-induced oxytocin and prolactin release d peripherally reducing mammary blood flow.[58] Metoclopramide, a pamine agonist, is used to stimulate lactation and is concentrated in k because of ion trapping. Neonatal plasma prolactin concentrations y be elevated following maternal administration of metoclopramide.[59] e oxytocin, prostaglandin $F_2\alpha$ administered intranasally increases milk ction.[60] Fenugreek is an herbal product used in human medicine[61-63] l has been shown to have oxytocic activity in animals.[64] Although the of herbal products seems to be increasing because they are viewed as r or more natural alternatives to pharmaceutical products, the potential sts for herbal products to have all of the properties of pharmaceuticals, ging from clinical usefulness to toxicity.

CONCLUSION

While the majority of pregnant or lactating patients are healthy and administration can be avoided, acute disorders such as infection require short-term medical treatment. Few pharmacokinetic studies of absorption, metabolism, distribution, and elimination during pregnan lactation exist specifically for canids and felids. Information to modif schedules to ensure efficacy and minimize the risk of toxicity is defi necessary. Whenever drugs are used in pregnant and lactating patient prescribing clinician must explain the relative benefits and risks assoc with the treatment and obtain an informed consent from the owner.

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