3
Perinatal Pharmacology
▼

Perinatal pharmacology involves the three most important participants in pregnancy: the mother, the placenta, and the fetus (Fig. 3-1). Virtually all drugs administered to the mother can traverse the placenta and appear in the fetal circulation to some extent. Hence an appreciation of perinatal pharmacology is important for the safe conduct of obstetric anesthesia.
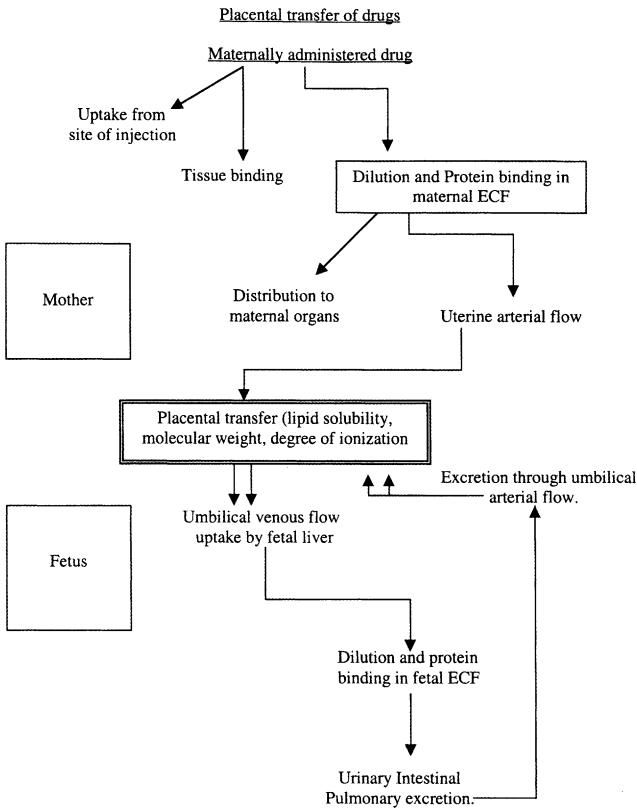
Placental transfer of drugs

Maternally administered drug

Uptake from
site of injection

Tissue binding

Dilution and Protein binding in
maternal ECF

Mother

Distribution to
maternal organs

Uterine arterial flow

Placental transfer (lipid solubility,
molecular weight, degree of ionization)

Excretion through umbilical
arterial flow.

Umbilical venous flow
uptake by fetal liver

Fetus

Dilution and protein
binding in fetal ECF

Urinary Intestinal
Pulmonary excretion.

Figure 3-1. Drug disposition in the mother, placenta, and fetus.

General Principles

Maternal drug administration can affect the fetus in two ways: (1) a direct fetal effect, via transplacental passage into the fetal circulation, and (2) an indirect effect, by affecting uteroplacental blood flow. The latter is discussed in Chapter 5.

Substances in the maternal circulation can cross the placenta by one of four mechanisms. The majority of substances are subject to *passive diffusion*, in which the compound flows across lipid membranes down a concentration gradient. The degree of flow is proportional to the concentration difference between the maternal and fetal circulations, and is affected by a number of factors discussed in detail below. Some substances are subject to *facilitated diffusion*, in which a carrier protein in the lipid membrane aids passage of the substance, again down a concentration gradient. Glucose crosses from the maternal to fetal circulation in this way. *Active transport* refers to an energy-requiring process in which a transporter molecule moves the substance, often against a concentration gradient (i.e., from lower to higher concentration). A variant of this process is co-transport, in which the movement of one substance is linked to the movement of another, also in an energy-requiring step. Amino acids appear to cross from the maternal to fetal circulation in this way, co-transported with sodium. Finally, some large molecules, such as immunoglobulins, are transferred via *pinocytosis*, in which invaginations of cell membranes surround the molecule to form a vesicle that subsequently fuses with a cell in the other circulation and releases the molecules.

For substances subject to passive diffusion, the movement of the compound across the placenta can be described by the diffusion equation:

$$Q/t = \frac{KA(C_m - C_f)}{D} \tag{3-1}$$

where Q/t is the quantity of the drug transferred in a unit of time; K is a diffusion constant; A is the total diffusion area of the placenta; C_m and C_f are the maternal and fetal concentration of free drugs, respectively; and D is the diffusion distance across the placenta. Factors that alter the amount present in the fetal circulation include those that affect the maternal concentration (C_m), factors related to the substance and its interaction with the placenta (K, A, and D), and factors related to fetal handling of the substance (C_f).

The Mother

Site of Administration

The maternal plasma concentration of any agent will depend upon the site of administration as well as the amount of agent administered. In the case of local anesthetics, the highest to lowest maternal plasma concentration will be achieved by the following routes of administration: intravenous > paracervical > caudal epidural > lumbar epidural > intramuscular > subarachnoid block.[1]

Addition of Epinephrine

Epinephrine can slow the absorption of local anesthetics injected subcutaneously or epidurally. It has been shown to reduce the peak maternal plasma concentration of lidocaine and mepivacaine.[1] However, epinephrine has an insignificant effect on peak concentrations of bupivacaine.

Maternal Volume of Distribution and Clearance

The volume of distribution for many drugs is increased in pregnancy, likely due to an increase in plasma volume and body fat. However, clearance of some drugs may be decreased (thiopental), unchanged (succinylcholine), or increased (vecuronium). Because sensitivity to many anesthetic drugs is increased in pregnancy (inhalation anesthetics, thiopental, vecuronium, local anesthetics), smaller doses may be administered to achieve the same clinical effect as in nonpregnant women, reducing the maternal blood concentration attained.

Ester drugs such as 2-chloroprocaine, succinylcholine, and remifentanil are metabolized by plasma cholinesterases; hence the maternal plasma half-life of these drugs is very short, and less drug will ultimately reach the fetus. Conversely, some drugs have long-lived metabolites which can reach the fetus. For example, normeperidine, a metabolite of meperidine, is twice as toxic as the parent compound but only half as analgesic. This metabolite is cleared only slowly by the fetus.[2,3] Infants born

more than 4 h after maternal meperidine may be depressed due to accumulation of normeperidine in their tissues.

Uteroplacental Blood Flow

Maternal blood must enter the uteroplacental circulation for substances to cross the placenta into the fetus. Factors that increase or decrease blood flow may alter transport of various substances, particularly those with flow-limited, as opposed to diffusion-limited transport.[4] In addition, during uterine contraction, when blood flow is reduced or halted, transport will be sharply reduced; if maternal drug concentrations decline during the interval of reduced flow, overall transport may be reduced.

Maternal Protein Binding

Plasma protein binding may be important for placental transfer. It is the free drug, not the protein-bound fraction, that is in equilibrium across the placenta. However, protein binding differs markedly among drugs, and fetal protein binding is only about 50% of that in the mother. Therefore, highly protein-bound drugs (such as bupivacaine) will exist in much higher total concentrations in the mother than the fetus, as measured by the fetal:maternal plasma ratio or umbilical vein to maternal vein (UV/MV) concentration ratio. The effect of protein binding on the rate of transfer of drugs is less clear. It appears that free and bound drugs are in rapid equilibrium, so such binding should have a minimal effect.

Maternal pH and Drug pKa

Highly charged drugs cross the lipid membranes of the placenta inefficiently. Therefore, ionizable drugs with a pKa close to the body's pH of 7.4 will exist in a greater fraction in the nonionized form in maternal blood, and this will be associated with higher placental transfer. For example, mepivacaine with a pKa of 7.6 will cross the placenta in higher amounts when compared with bupivacaine with a pKa of 8.1 or the closely related ropivacaine and levobupivacaine. Conversely, maternal pH changes due to metabolic or respiratory disorders, or due

to hyperventilation-induced alkalosis, may alter the available fraction of a drug available for placental transfer.

The Placenta

Area of Transfer and Diffusion Distance

The rate of drug transfer depends upon the effective area of transfer. The maternal part of the placenta contains 180–320 spiral arteries. The functional unit of the placenta is the "placentone," which is supplied by a single spiral artery. It has been speculated that placental abnormalities, such as cocaine-induced edema, chorioamnionitis, or preeclampsia, may alter the diffusion distance (see Equation 3-1). The clinical significance of these changes is unclear.

Molecular Weight and Spatial Configuration of Drugs

Drugs with a molecular weight less than 500 daltons (Da) will freely cross the placenta. Drugs above 500 Da will cross with difficulty, and most drugs above 1,000 Da will not cross the placenta in appreciable amounts.[5] Most clinically useful drugs will cross the placenta because of their low molecular weight. However, heparin and protamine do not cross the placenta because of their large molecular weight (MW). Highly ionized drugs generally cross the placenta less easily. However, there are exceptions to these rules, and large drugs (e.g., vancomycin, MW = 1449 Da) and charged drugs (e.g., ampicillin) do sometimes cross the placenta readily.[6]

Protein Binding and Lipid Solubility of Drugs

Drugs bound to plasma protein were previously thought to cross the placenta with great difficulty (as inferred by the fetal:maternal ratio). However, more recent data suggest these drugs rapidly equilibrate with the free form, and protein binding may not appreciably affect placental transfer.[5] Lipid solubility eases the transfer of drugs through the placenta. Highly lipid-soluble drugs, such as barbiturates, can reach the

fetus in large amounts after easy placental transfer. However, some drugs with very high lipophilicity such as sufentanil may become bound in the lipid membranes of the placenta itself, reducing total transfer to the fetus.[7]

Metabolism of Drugs

The placenta can manufacture and excrete specific enzymes, including many subtypes of the cytochrome P450 system, that will destroy maternally administered drugs.[8] A common clinically relevant example is prednisone, which is metabolized by the placenta and therefore appears in minute concentrations in the fetus.

The Fetus

Fetal uptake, distribution, and metabolism and elimination will ultimately be responsible for the fetal drug concentration and its effect on the fetus. Once drugs reach the fetus, several important factors will determine the free umbilical artery concentration of drugs.

Uptake

Fetal uptake of drugs will depend on protein binding, lipid solubility, and the pKa of the drugs. Because of lesser amount of total protein in the fetus, plasma protein-binding capacity in the fetus is less than in the mother. As noted, total plasma concentration will be lower than in the mother for highly protein-bound drugs, but free drug concentrations will be approximately equal at equilibrium. Highly lipid-soluble drugs (e.g., bupivacaine) will redistribute within the fetus as they do in the adult. Finally, and most importantly, fetal pH can play a significant role in determining the amount of drug in the fetus at equilibrium. Normal fetal pH varies between 7.32 and 7.38, whereas maternal pH varies between 7.38 and 7.42. In a normal situation, maternal fetal transfer of the drug will depend mostly on the concentration gradient. However, if the fetus is acidemic, then un-ionized drugs from the mother will cross the placenta and be preferentially protonated to the ionized (charged) form. Because the ionized form crosses the placenta

less efficiently, the *ionized form of drugs will get "trapped" and accumulate in the fetus. This phenomenon has been described as "ion trapping" and to avoid it chloroprocaine is recommended for epidural anesthesia when the fetus is suspected to be acidotic.*[9,10]

Distribution

Drugs enter the fetal circulation via the umbilical vein and redistribute within the fetus as they do in the adult (Fig. 3-2). The umbilical arterial concentration of drugs will frequently be lower than that of the umbilical vein, and it may better reflect the concentration in critical organs such as the brain and heart.

Fetal Liver

The umbilical vein blood from the placenta either reaches the liver or flows through the ductus venosus. The left lobe of the liver is transfused by umbilical venous blood, whereas the right lobe is perfused by portal venous blood. Because UV blood-containing drugs will pass through the liver before entering the systemic circulation, the fetal liver helps in extracting substantial amounts of drug entering the fetus and thereby helps in protecting the fetal brain. For example, thiopental administered intravenously to the mother is taken up by the fetal liver in a significant amount.[11]

Progressive Dilution of Umbilical Vein in Blood Concentration

Umbilical vein blood passing through either the fetal liver or the ductus venosus will ultimately be diluted by the blood received from the lower extremities or gastrointestinal tract.

Extensive Right-to-Left Shunt of the Fetal Circulation

After reaching the fetal heart, approximately 57% of fetal cardiac output returns to the placenta without perfusing fetal
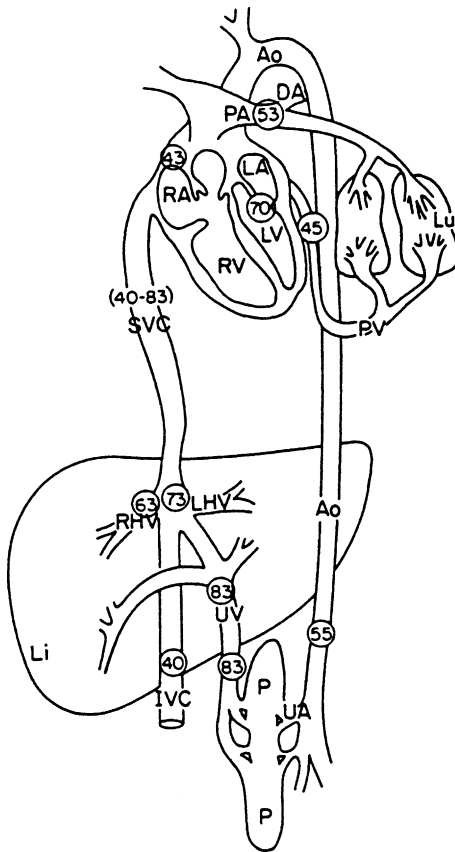
Figure 3–2. Fetal circulation (numbers indicate percent saturation). IVC = inferior vena cava; P = placenta; Li = liver; RHV, LHV = right and left hepatic veins; SVC = superior vena cava; RA, LA = right and left atria; DA = ductus arteriosus; PA = pulmonary artery; Ao = aorta; Lu = lung; DV = ductus venosus; PV = pulmonary vein; UV = umbilical vein; UA = umbilical artery. (From Martin.[12])

tissues. This is related to extensive shunting of the fetal circulation via the foramen ovale of the heart as well as the ductus arteriosus. This mechanism leads to diminished exposure of the fetal brain to circulating drugs.

Summary

Clinically, the above mechanisms help explain why after thiopental administration to the mother for cesarean section, a vigorous crying infant may be delivered from a sleeping mother. It is also reassuring that the fetus may be unaffected when lower doses of maternal sedatives are required during regional anesthesia for labor or operative delivery.

In summary, the majority of maternally administered drugs will cross the placenta and reach the fetus, but because of the unique fetal circulation, reduced amounts of the drugs will reach the fetal brain and myocardium.

References

1. Rosenberg PH, Veering BT, Urmey WF. Maximum recommended doses of local anesthetics: a multifactorial concept. *Reg Anesth Pain Med*. 2004;29(6):564–575; discussion 524.
2. Kuhnert BR, Kuhnert PM, Philipson EH, Syracuse CD. Disposition of meperidine and normeperidine following multiple doses during labor. II. Fetus and neonate. *Am J Obstet Gynecol*. 1985;151(3):410–415.
3. Kuhnert BR, Philipson EH, Kuhnert PM, Syracuse CD. Disposition of meperidine and normeperidine following multiple doses during labor. I. Mother. *Am J Obstet Gynecol*. 1985;151(3): 406–409.
4. Barry JS, Rozance PJ, Anthony RV. An animal model of placental insufficiency-induced intrauterine growth restriction. *Semin Perinatol*. 2008;32(3):225–230.
5. Pacifici GM, Nottoli R. Placental transfer of drugs administered to the mother. *Clin Pharmacokinet*. 1995;28(3):235–269.
6. Pacifici GM. Placental transfer of antibiotics administered to the mother: a review. *Int J Clin Pharmacol Ther*. 2006;44(2):57–63.

  7. Krishna BR, Zakowski MI, Grant GJ. Sufentanil transfer in the human placenta during in vitro perfusion. *Can J Anaesth*. 1997;44(9):996–1001.

  8. Syme MR, Paxton JW, Keelan JA. Drug transfer and metabolism by the human placenta. *Clin Pharmacokinet*. 2004;43(8):487–514.

  9. Biehl D, Shnider SM, Levinson G, Callender K. Placental transfer of lidocaine: effects of fetal acidosis. *Anesthesiology*. 1978;48(6):409–412.

 10. Philipson EH, Kuhnert BR, Syracuse CD. Fetal acidosis, 2-chloroprocaine, and epidural anesthesia for cesarean section. *Am J Obstet Gynecol*. 1985;151(3):322–324.

 11. Finster M, Morishima HO, Mark LC, Perel JM, Dayton PG, James LS. Tissue thiopental concentrations in the fetus and newborn. *Anesthesiology*. 1972;36(2):155–158.

 12. Martin R. Prepartum and intrapartum fetal monitoring. In: Datta S, ed. *Anesthetic and Obstetric Management of High-Risk Pregnancy*. 3rd ed. New York, NY: Springer; 2004