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PHARMACOKINETICS IN THE OVINE MATERNAL-FETAL UNIT

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INTRODUCTION

Our primary concern in the use of drugs during pregnancy is the adverse effects that these drugs may produce on the developing fetus. It is now evident that the placenta does not act as a "barrier" to protect the fetus against exposure to most drugs consumed by the mother during pregnancy. The intensity of drug effects in the fetus or the neonate is a function of the extent of fetal exposure to the drug following maternal administration, and the pharmacodynamic actions of the drug on the mother and fetus. For drugs which have similar pharmacodynamic actions in the maternal-fetal unit, the magnitude of pharmacologic effects will be greatly influenced by the pharmacokinetics of their disposition in the maternal-fetal unit.

Information on maternal-fetal pharmacokinetics in humans has been restricted for both technical and ethical reasons, and available data are limited to single time point determinations of maternal and fetal drug concentrations at the time of delivery. Serial determinations of maternal and fetal drug concentrations over time are also not practical in the smaller laboratory animals.

Most of the currently available information on maternal-fetal pharmacokinetics has been obtained using the pregnant ewe. The major advantage of the ewe is the relatively large size of the fetus. The fetal lamb in the third trimester is large enough to permit the implantation of catheters in the fetal blood vessels, making it possible to obtain fetal blood samples without sacrificing the animal. Initially, most studies were carried out with the ewe under anesthesia. However, increasing recognition that maternal

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anesthesia may affect uterine perfusion and fetal cardiovascular function (1) has led to the use of the chronic preparation (2–4). In the chronic preparation, all maternal and fetal vascular catheters are tunneled subcutaneously to the maternal flank and stored in a pouch. The animals are then allowed several days of recovery from surgery before any pharmacokinetic studies are carried out. The chronic indwelling catheters permit repeated sampling of fetal and maternal blood in an unanesthesized animal. For a detailed discussion of the advantages of the chronic pregnant ewe model and the surgical procedures, the reader is referred to recent publications by Van Petten et al (4) and Rudolph & Heymann (5).

Several recent reviews have discussed the factors which influence the rate of drug transfer from mother to fetus (6–9), and these will not be discussed in this review. This review will primarily consider the pharmacokinetic modeling of the maternal-fetal unit, and the support for and validation of these pharmacokinetic models with experimental data that have been obtained using the pregnant ewe model. This review will also discuss the factors which are important in determining the extent of fetal exposure to a maternally-administered drug, and the criteria that should be used in evaluating the relative safety of a drug for the fetus.

PHARMACOKINETIC CONSIDERATIONS

The development of any pharmacokinetic model involves three separate stages. The first is the development of a plausible model for the particular biological system. This generally requires considerable knowledge of the anatomical and physiological processes of the real biological system. Given a specific compartmental model, the second step is the derivation of the mathematical expressions describing such a system. The last, and usually the most difficult, is the collection of experimental data, and the calculation of the parameter estimates. The proposed model must then be tested for goodness-of-fit by comparing the experimental data with theoretical estimates.

Usually the simplest, most reasonable, model is first proposed. If the experimental data are not consistent with theoretical estimates, another more complex model is proposed and tested. This procedure continues until a good fit is obtained between the experimental data and the theoretical estimates.

It is important to realize that any pharmacokinetic model is only a simplification of the real biological system, and the development of more complicated models provides a closer approximation to reality. The complexity of the model, however, is limited by the experimental data that can be obtained. Several different models may be consistent with a particular set of experimental data, and the final selection of a particular model

depends on whether parameter values can be estimated with sufficient precision for the intended purpose. Therefore, the simplest model that is consistent with the experimental data, and which allows adequate predictions to be made regarding the biological system, should be selected. An outline of the essential steps for constructing compartmental models has been presented by Berman (10), and more detailed discussions of the various steps can be found in his earlier publications (11, 12).

Anatomical and Physiological Considerations

In the maternal-fetal unit, a maternally-administered drug is transferred from the placenta to the fetus via the umbilical vein, and returned from the fetus to the placenta via the umbilical artery. Therefore, the simplest model of the maternal-fetal unit would be a two-compartment model wherein the mother and fetus are each represented as a single compartment, with bidirectional drug transfer between the two compartments. As illustrated in Figure 1, there are three possible types of two-compartment models. They differ only in that the drug may be eliminated from the maternal compartment only (Model 1a), from the fetal compartment only (Model 1b), or from both maternal and fetal compartments (Model 1c).

Since it is highly unlikely that a drug should be eliminated by the fetus and not by the mother, Model 1b need not be considered any further. Most investigators have proposed Model 1a based on the assumption that the fetus does not have significant ability to eliminate drugs. This assumption

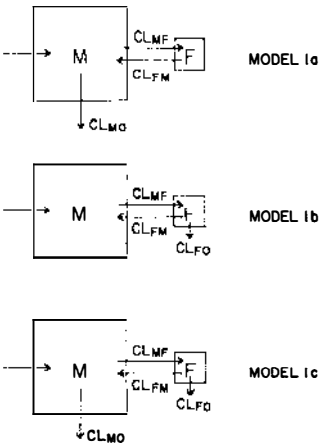

Figure 1 Three possible types of two-compartment open models describing the disposition of a drug in the mother and the fetus at steady state, where M represents the maternal compartment, and F represents the fetal compartment; CL_{MF} and CL_{FM} are the respective clearances from the maternal to the fetal compartment, and from the fetal to the maternal compartment; CL_{MO} and CL_{FO} are the respective nonplacental clearances from the maternal and fetal compartments.

is based on the early findings that the fetus of many animal species is deficient in both the cytochrome P-450-linked electron transport chain and related enzyme activities (13, 14). The rat, mouse, guinea pig (15), and rabbit (16, 17) have all been found to have very low capacity to oxidize drugs and other foreign compounds until after birth. More recent studies, however, have shown that the human fetal liver (18–21) and the fetal liver of certain nonhuman primates (22–25) contain cytochrome P-450 and demonstrate drug-metabolizing capacity by mid-gestation. These later findings suggest that Model 1c may be a more suitable model for describing drug disposition in the maternal-fetal unit of certain species.

Mathematical Considerations

In the following discussion, all drug distribution and elimination processes are assumed to follow first order kinetics.

MODEL 1a If a drug is administered as an intravenous bolus to the maternal compartment in such a model, the change in amount of drug with time in the maternal and fetal compartments can be described as follows:

$$\frac{dX_M}{dt} = CL_{FM}c_F - (CL_{MF} + CL_{MO})c_M \quad (1)$$

$$\frac{dX_F}{dt} = CL_{MF}c_M - CL_{FM}c_F, \quad (2)$$

where X_M and X_F are the respective amounts of drug in the mother and fetus; and c_M and c_F are the respective drug concentrations in the mother and fetus. The clearance terms are defined as follows: CL_{MF} is the volume of maternal plasma totally cleared of the drug by the placenta per unit time, CL_{MO} is the volume of maternal plasma totally cleared of the drug by nonplacental mechanisms per unit time, and CL_{FM} is the volume of fetal plasma totally cleared of the drug by the placenta per unit time.

If the drug is administered to the mother at a constant infusion rate J, a steady state will eventually be attained in the mother when the rate of infusion equals the rate of elimination from the maternal compartment. Similarly, a steady state will be attained in the fetus when the rate of drug input into the fetal compartment equals the rate of elimination from the fetal compartment. At steady state, equations 1 and 2 become,

$$\frac{dX_M}{dt} = J + CL_{FM}c_F - (CL_{MF} + CL_{MO})c_M = 0 \quad (3)$$

$$\frac{dX_F}{dt} = CL_{MF}c_M - CL_{FM}c_F = 0, \quad (4)$$

where c_M and c_F are the respective steady state drug concentrations in the mother and fetus.

Since the fetal compartment is closed in this model (i.e. there is no elimination from that compartment to the exterior), the intercompartmental clearances must be equal ($CL_{MF} = CL_{FM}$), and the fetal steady state drug concentration is the same as maternal steady state drug concentration (26, 27). Therefore, upon chronic infusion of the drug to the mother, an equilibrium must eventually be reached between mother and fetus, and there is no further net transfer of drug between the two compartments. It should be noted that the permeability of the placenta does not influence this maternal:fetal equilibration. Fetal plasma drug concentration must equal maternal drug concentration at steady state irregardless of the rate of drug transfer across the placenta. The rate of placental transfer will only determine the time needed to approach maternal:fetal equilibrium (28).

MODEL 1c The rate equation that describes the amount of drug in the maternal compartment is identical to that derived for Model la (equation 1). The corresponding equation for describing the amount of drug in the fetal compartment as a function of time is as follows:

$$\frac{dX_F}{dt} = CL_{MF}c_M - (CL_{FM} + CL_{FO})c_F, \quad (5)$$

where CL_{FO} is the volume of fetal plasma totally cleared of the drug by nonplacental mechanisms per unit time.

If the drug is infused into the mother at a constant infusion rate J, then the following steady state equations apply:

$$\frac{dX_M}{dt} = J + CL_{FM}c_F - (CL_{MF} + CL_{MO})c_M = 0 \quad (3)$$

$$\frac{dX_F}{dt} = CL_{MF}c_M - (CL_{FM} + CL_{FO})c_F = 0. \quad (6)$$

A steady state will be reached in the maternal-fetal unit when the rate of drug infusion to the mother is just equalled by the total rate of loss from both maternal and fetal compartments ($CL_{MO}c_M + CL_{FO}c_F$). At this steady state, the rate of drug entry into the fetal compartment ($CL_{MF}C_M$) must exceed the rate of drug transfer from the fetal compartment to the maternal compartment ($CL_{FM}c_F$) by an amount equal to the rate of drug elimination from the fetal compartment ($CL_{FO}c_F$) (see equation 6). Since a net flux of drug persists from the maternal to the fetal compartment, an equilibrium between the two compartments can never be achieved, and fetal drug concentration will always be lower than maternal drug concentration. Hence even though the entire maternal-fetal unit can approach a steady

state, wherein maternal and fetal drug concentrations remain constant, it does not approach a state of equilibrium (26).

In the past, it was often thought that if fetal drug concentration was lower than maternal drug concentration at steady state, it would imply that there was a "placental barrier" limiting diffusion of the drug from mother to fetus. However, the mathematical considerations presented above suggest that a fetal : maternal steady state concentration ratio of less than one could only result from elimination of the drug by the fetus. This fetal : maternal concentration ratio was predicted by the computer simulations of Levy & Hayton (29) and Gillette (30). Some investigators have suggested that a lower fetal drug concentration may be due to metabolism of the drug by the placenta.

Experimental Data on Maternal-Fetal Drug Distribution

The distribution of several drugs between the mother and fetus at steady state has been studied using the pregnant ewe model. The results of these studies are summarized in Table 1. For all drugs studied, fetal steady state drug concentration was found to be lower than the corresponding maternal steady state drug concentration, resulting in a fetal : maternal steady state concentration ratio of less than one.

These results show that despite steady state conditions in both maternal and fetal compartments, equilibrium was not achieved between the two compartments. For some drugs, this observed maternal : fetal concentration gradient may, in part, be due to differences in the extent of drug binding in maternal and fetal plasma. The binding of acetylsalicylic acid (31),

Table 1 The ratio of fetal plasma drug concentration to maternal plasma drug concentration at steady state

Drug	$\bar{c}_F/\bar{c}_M$[a]	Reference
Acetylsalicylic acid	0.22	Anderson et al (31)
Antipyrine	0.90	Shoeman et al (32)
Dexamethasone	0.67	Anderson et al (33)
Dilantin	0.51	Shoeman et al (32)
Indomethacin	0.28	Anderson et al (34)
Lidocaine	0.76	Biehl et al (35)
	0.79	Morishima et al (36)
Meperidine	0.30	Szeto et al (37)
Methadone	0.15	Szeto et al (38)
	0.18	Szeto et al (38a)
Morphine	0.13	Szeto et al (38a)
Nitroprusside	0.87	Naulty et al (39)
Triamterene	0.17	Pruitt et al (40)

[a] Fetal: maternal steady state drug concentrations

dexamethasone (33), and indomethacin (34) was found to be similar in maternal and fetal plasma. Thus differential binding cannot account for the maternal:fetal concentration gradient of these drugs. Although both meperidine and methadone are bound to a lesser extent in fetal plasma (37, 38, 38b), the differences are not sufficient to account for the maternal:fetal concentration gradients at steady state. The large maternal:fetal concentration gradient for morphine also cannot be explained by protein binding since its binding is negligible in both maternal and fetal plasma (38a). Although protein binding data are not currently available for the other drugs listed in Table 1, these experimental results would appear to support Model 1c rather than Model 1a for the disposition of many drugs in the ovine maternal-fetal unit.

Experimental Evidence for Fetal Drug Elimination

Several attempts have been made to obtain direct evidence for fetal drug elimination in support of Model 1c. Drug elimination in the fetus may occur via renal excretion and/or biotransformation. Therefore, the total nonplacental clearance of drug from the fetal compartment (CL_{FO}) should be the sum of renal clearance and clearance due to biotransformation.

RENAL CLEARANCE Surgical techniques have been developed for the cannulation of the fetal lamb bladder, making it possible to study urinary excretion of drugs and metabolites by the fetus in utero (41, 42). Using an acute preparation, Basso et al (43) were able to quantitate mannitol in fetal urine following a single intravenous bolus to the mother. The concentration of mannitol in fetal urine was almost ten fold higher than that in fetal plasma. Using a chronic preparation, Szeto et al (42) reported that the rate of excretion of meperidine into fetal urine is directly proportional to the amount of meperidine in fetal plasma. Furthermore, there is evidence that meperidine is secreted across the renal tubules by the mechanism of "ion trapping" (44). Renal clearance of lidocaine is lower and can be accounted for by filtration alone (45).

In the fetal lamb, urine is excreted into the amniotic sac and allantoic sac. Thus indirect evidence for urinary excretion of drugs can be obtained by the presence of drug in these fluids. Both mannitol (43) and meperidine (37) are detectable in amniotic fluid following maternal administration. In addition, phenytoin (32) and salicylates (46) have also been detected in amniotic fluid of the pregnant goat. The presence of drug in amniotic fluid, however, does not provide direct evidence for fetal urinary drug excretion since drug in amniotic fluid may also result from diffusion across the chorio-allantoic membranes. Indeed, it has been shown that meperidine can still be detected in amniotic and allantoic fluid despite ligation of the urethra and urachus to prevent urine flow into these fluid sacs (42).

CLEARANCE DUE TO BIOTRANSFORMATION Direct in vivo evidence for fetal drug biotransformation is much more difficult to obtain. Most information on fetal biotransformation in other animal species has come from in vitro studies of drug metabolizing enzymes, but such information is not available for the fetal lamb. The presence of metabolites in fetal plasma alone does not imply that the fetus has biotransformation ability since some metabolites of maternal origin may be readily distributed to the fetus (37). Recently Marshall et al (47) reported on the biliary excretion of propranolol in the fetal lamb. An indwelling catheter in the bile duct allowed the collection of bile from the fetus at various times after drug administration to the fetus, and their results showed that biliary clearance of propranolol in the fetus is similar to that in the mother.

PRESYSTEMIC DRUG ELIMINATION IN THE FETUS In the fetus, as much as 50% of umbilical venous blood flow is distributed to the fetal liver while the remaining blood is shunted through the ductus venosus into the right atrium (48, 49). As a result of this anatomic arrangement, up to 50% of the drug transferred across the placenta from the mother may undergo hepatic biotransformation prior to reaching the systemic circulation. Propranolol has been shown to undergo significant presystemic elimination in the fetal lamb. Marshall et al (47) found that biliary clearance of propranolol in the fetus was two- to threefold higher following maternal drug administration compared to following direct drug administration to the fetus. Therefore, for drugs with high hepatic extraction rates, presystemic elimination should be considered in the pharmacokinetic modeling of the maternal-fetal unit.

Experimental Determination of Placental and Nonplacental Drug Clearances in the Maternal-Fetal Unit

The total clearance of drugs from the fetus is the sum of placental clearance (CL_{FM}) and fetal nonplacental clearance (CL_{FO}). Until recently, little attention had been given to the study of the relative contribution of placental clearance versus fetal clearance in the overall clearance of a drug from the fetus.

Placental clearance of many substances has been measured utilizing the principles of Fick's Law of Diffusion (50). This technique, however, can only be used to study nonprotein bound, nonmetabolized substances which are cleared rapidly by the placenta and result in a measurable arteriovenous concentration difference across the placenta. It is, therefore, not applicable to the study of most drugs in the maternal-fetal unit.

If drug disposition in the maternal-fetal unit can be represented by compartmental model 1c (as illustrated in Figure 1), then it is theoretically possible to calculate placental and nonplacental drug clearance from the

mother and fetus utilizing steady state compartmental analysis. The practical requirement is that it must be possible to administer the drug to both mother and fetus, and to determine the steady state plasma drug concentration in both mother and fetus. The pregnant ewe model with chronic indwelling catheters in both mother and fetus is therefore ideal for such studies.

The drug is first administered at a constant infusion rate, J, to the mother, and maternal and fetal plasma drug concentrations at steady state are determined. The maternal and fetal plasma drug concentrations at steady state can be described by the following equations:

$$\frac{dc_M}{dt} = \frac{1}{V_M}[J + CL_{FM}c_F - (CL_{MF} + CL_{MO})c_M] = 0 \quad (8)$$

$$\frac{dc_F}{dt} = \frac{1}{V_F}[CL_{MF}c_M \quad (CL_{FM} + CL_{FO})c_F] = 0, \quad (9)$$

where V_M and V_F are the respective volumes of distribution in the mother and fetus. The drug is then administered at a constant infusion rate, J', to the fetus, and steady state plasma drug concentrations in the mother (c_M') and fetus (c_F') are determined. The maternal and fetal plasma drug concentrations at steady state under these conditions can be described as follows:

$$\frac{dc_M}{dt} = \frac{1}{V_M}[CL_{FM}c_F' - (CL_{MF} + CL_{MO})c_M'] = 0 \quad (10)$$

$$\frac{dc_F}{dt} = \frac{1}{V_F}[J' + CL_{MF}c_M' - (CL_{FM} + CL_{FO})c_F'] = 0. \quad (11)$$

With the above four equations (8–11), and experimentally-determined values for J, J', c_M, c_F, c_M' and c_F', it is then possible to calculate all four clearance rates:

$$(CL_{MF} + CL_{MO}) = \frac{J}{c_M - c_F(c_M'/c_F')} \quad (12)$$

$$(CL_{FM} + CL_{FO}) = \frac{J'}{c_F' - c_M'(c_F/c_M)} \quad (13)$$

$$CL_{MF} = (CL_{FM} + CL_{FO})(c_F/c_M) \quad (14)$$

$$CL_{FM} = CL_{MF} + CL_{MO})\,(c_M'/c_F'). \quad (15)$$

This steady state compartmental method therefore allows the determination of placental and fetal drug clearances without making any assumptions regarding the mechanism or extent of drug transfer between the maternal and fetal compartments. In contrast, the compartmental method proposed recently by Anderson & co-workers (31, 33, 34) assumes that drug transfer between the two compartments occurs only by diffusion, and that the bidirectional placental clearances are equal.

Two practical considerations should be taken into account regarding the use of this method. First of all, the maternal and fetal drug infusions should ideally be carried out concurrently in the same animal. To simultaneously quantitate the concentrations of drug originating from both the maternal and fetal infusions, it would be necessary to use a method such as double isotope labeling, or stable isotope labeled drug administration followed by detection utilizing selected ion monitoring (51). If it is not possible to utilize such methods, then it is necessary to carry out the maternal and fetal infusions on two separate days. To minimize any changes in the factors that may influence transplacental drug diffusion (such as uterine and umbilical blood flow), the chronic, unanesthesized, unrestrained pregnant ewe preparation should be used.

The second point of consideration is that all calculations should be made using free unbound drug concentrations only. This is important because the extent of drug binding to maternal and fetal plasma proteins may be significantly different (37, 38, 38b).

The clearances of morphine and methadone have been determined using this compartmental method with the chronic pregnant ewe model (38a). The results are summarized in Table 2. With a constant rate infusion to the mother, the ratio of fetal : maternal steady state free drug concentration was found to be 0.13 for morphine and 0.34 for methadone. The calculated clearance values show that the clearance of morphine from mother to fetus is much slower than the clearance of methadone from mother to fetus. The more limited diffusion of morphine across the placenta can be accounted for by the very low apparent partition coefficient, P', of morphine as compared to methadone (52). Although morphine is also eliminated by the

Table 2 Placental and nonplacental clearances of morphine and methadone from the maternal and fetal compartments

	CL_{MO} (ml/min)	CL_{MF} (ml/min)	CL_{FM} (ml/min)	CL_{FO} (ml/min)	$\frac{CL_{FO}}{(CL_{FM} + CL_{FO})}$ (%)
Morphine (n = 7)	2797 ± 247	24.9 ± 3.0	58.4 ± 7.1	125.6 ± 15.3	67.4 ± 3.9
Methadone (n = 7)	7571 ± 865	390.3 ± 92.8	504 ± 86.3	381.0 ± 89.1	42.8 ± 4.9

fetus, fetal nonplacental clearance of morphine is lower than that of methadone. Therefore the lower extent of fetal exposure to morphine as compared to methadone is primarily due to a slower clearance of morphine across the placenta from mother to fetus, rather than a more rapid clearance of morphine by the fetus. Because of the slow clearance of morphine across the placenta from fetus to mother, the fetus plays a more important role in the overall elimination of morphine from the fetal compartment.

It is very important to point out that this simple two-compartment model is only adequate for describing maternal and fetal drug disposition under steady state conditions. At steady state, the distribution of a drug between all body tissues can be assumed to be complete, and the mother and fetus can each be treated kinetically as a single homogenous unit. This simple model, however, may not be adequate under non-steady-state conditions. Most drugs require a finite time to distribute fully throughout the body, and the rates of distribution to the various tissues are not equal. It has generally been found that a two or more compartment model is necessary to adequately describe the time-course of distribution and elimination of a drug in the body. For this reason, it is important that the drug should always be administered to mother and fetus as a continuous infusion when calculating placental and nonplacental clearances, rather than as an intravenous bolus as proposed by Anderson et al (31, 33, 34).

The Need for More Complex Pharmacokinetic Models

If it is necessary to describe the kinetics of drug distribution and elimination within the mother and fetus under non-steady-state conditions, more complex pharmacokinetic models may be necessary.

MATERNAL DISTRIBUTION KINETICS The distribution of several drugs has been studied following a single intravenous bolus to the pregnant ewe, including bupivacaine (53), butorphanol (54), digoxin (55), lidocaine (36), meperidine (37), methadone (38), and propranolol (47). In addition, we have also recently studied the disposition of morphine and acetylmethadol in the pregnant ewe (H. H. Szeto et al, unpublished data). In all cases, the plasma decay curve in the mother was found to be biexponential, suggesting that the disposition of these drugs should be described by a two-compartment model with a central compartment representing the more rapidly-perfused tissues, and a peripheral compartment representing the remaining tissues. In this case, the maternal-fetal unit can be represented by the three-compartment model in Figure 2 (Model 2). Since the drug-eliminating organs (e.g. liver and kidneys) are generally considered to be part of the rapidly-perfused central compartment (M_c), the peripheral com-

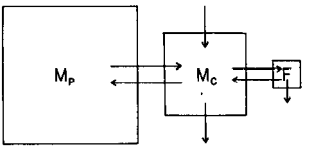

Figure 2 A three-compartment open model describing the disposition of a drug in the mother and fetus under non-steady-state conditions.

partment of the mother (M_p) is represented as a closed compartment. For reasons discussed earlier, the fetal compartment is represented as an open compartment.

Since the volume of distribution of the fetal compartment is so small relative to the two maternal compartments, distribution of the drug to the fetal compartment will most likely not be reflected in the overall plasma decay curve of the mother. Therefore, even though it is a three-compartment system, the maternal plasma decay curve may only demonstrate a biexponential decline. In fact, the fetus can usually be included as part of the central or peripheral compartment of the mother.

When a drug is administered as an intravenous bolus to the mother, drug concentration in fetal plasma initially rises because of a positive maternal:fetal concentration gradient. At one instant in time the mother and fetus are momentarily in equilibrium with each other so that there is no net diffusion between them. At precisely this time, fetal drug concentration is at its maximum. As the drug continues to be cleared from the maternal compartment, the diffusion gradient is reversed, and fetal drug concentration will begin to fall.

Whether the fetus is considered part of the maternal central compartment or peripheral compartment depends on the rate of distribution of the drug between the mother and fetus. If the rate of distribution between mother and fetus is rapid relative to the other maternal tissues, the fetus may be considered part of the central compartment of the mother. For example, it has been shown that the fetal plasma decay curve of meperidine follows the maternal plasma decay curve more closely than the calculated concentration-time curve of the maternal peripheral compartment (37). The time to maternal-fetal equilibration is greatly influenced by the rate of drug clearance from the maternal compartment (56). The more rapidly the drug is cleared from the maternal compartment, the more rapidly maternal-fetal equilibration will take place. The rapid equilibration of meperidine and bupivacaine between mother and fetus is consistent with the rapid clearance of these drugs from the mother; their elimination half-lives are only in the order of 20–30 min (37, 53). The somewhat slower equilibration of digoxin (55), methadone (38), and butorphanol (54) between the mother and fetus may be accounted for by their slightly longer half-lives in the ewe.

For most drugs that have been investigated, distribution to the fetus appears to be very rapid, and the fetus can be considered part of the rapidly-perfused central compartment of the mother. This is really not so surprising, since in the last trimester, and especially near term, uterine blood flow is as high as 15% of cardiac output in the sheep (57). The percentage of cardiac output to the uterus is, therefore, as high as that to the brain, and is second only to the liver and kidneys.

Following an intravenous bolus of drug to the mother, the relationship between fetal drug concentration to maternal drug concentration is constantly changing because the drug is continuously being cleared by the mother and fetus. It must be emphasized that the relationship between fetal and maternal plasma drug concentrations in the post-distribution phase following an intravenous bolus does not indicate what the distribution would be at steady state. This was clearly demonstrated to be the case for meperidine (37). In the post-distribution phase following an intravenous bolus of meperidine to the mother, fetal plasma concentrations were similar to maternal plasma concentrations. However, following a constant rate infusion of meperidine to the mother, the ratio of fetal:maternal steady state concentration was only 0.3. The fetal:maternal concentration ratio is higher following an intravenous bolus because maternal drug concentration is falling continuously. The faster the drug is being cleared from the maternal compartment, the larger the discrepancy will be. This point deserves particular emphasis since much of the small laboratory animal data on fetal exposure to various drugs are obtained after single dose administration to the mother.

FETAL DISTRIBUTION KINETICS That the fetus should behave as a two-compartment system is supported by the findings that fetal plasma decay curves following a single intravenous bolus of acetylsalicylic acid (31), indomethacin (34), meperidine (37), lidocaine (45), or propranolol (47) to the fetus were all biexponential. A complete representation of the maternal-fetal unit should then consist of four compartments, as depicted in Figure 3 (Model 3). If drug elimination can be assumed to take place only from the central compartment, then the two peripheral compartments can be represented as closed compartments.

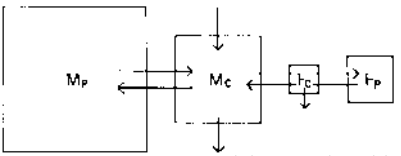

Figure 3 A four-compartment open model describing the disposition of a drug in the mother and fetus under non-steady-state conditions.

The reason that only two exponential declines can be delineated from the fetal plasma decay curve is because the volumes of the two maternal compartments are so large that they act as a sink for the drug, and it is not possible to distinguish the much smaller fetal peripheral compartment from these larger maternal compartments. It is very difficult to obtain experimental data that would support such an elaborate pharmacokinetic model. Furthermore, since the total volume of distribution in the fetus is very small relative to that of the mother, the number of fetal compartments will not have much influence on the overall disposition of a drug in the maternal-fetal unit. Therefore, the maternal and fetal plasma decay curves following maternal drug administration will be indistinguishable from those described by Model 2, and the proposal of such a complex model may not be necessary.

Although in a pharmacokinetic sense it may not be important to consider the need of a fetal peripheral compartment, it may be necessary when we are considering the time-course of pharmacologic effects in the fetus following maternal drug administration. The time-course of pharmacologic effect may be related to the drug concentration in any one of the compartments, depending on the site of action of the drug. If the site of action is in the central compartment, the time-course of effect will be related to the time-course of drug concentration in the central compartment. On the other hand, if the site of action is in the peripheral compartment, then the time-course of effect will be better related to the time-course of drug concentration in the peripheral compartment. It is, therefore, important to realize that the rate of distribution of a drug to all fetal tissues may not be uniform, and the time-course of drug concentration in fetal plasma may not reflect the time-course of drug concentration in all tissues.

The importance of understanding distribution kinetics in the fetus is well illustrated by the time-course of respiratory depression in the newborn following the administration of meperidine to the mother during labor. Many studies have failed to demonstrate a correlation between the incidence of neonatal respiratory depression and the concentration of meperidine in cord blood (58–62). Since meperidine is a narcotic analgesic which depresses respiration by virtue of a direct effect on the brain stem respiratory centers, one would expect the time-course of respiratory depression to be related to the time-course of meperidine in the central nervous system rather than in plasma. In a recent study using the chronic pregnant ewe model, the time-course of meperidine concentration in fetal plasma was compared with that in the fetal brain following intravenous and intramuscular administration of the drug to the mother (63). The time-course of meperidine concentration in the brain was estimated by measuring the arterio-venous concentration difference of meperidine across the fetal brain

as a function of time after drug administration. To achieve this, chronic indwelling catheters were placed in the fetal brachiocephalic artery and sagittal vein. The results showed that there is a lag time between peak plasma meperidine concentration and peak brain concentration. The lag time was found to be more significant following intramuscular administration. These findings suggest that for meperidine, the fetal brain should be considered part of the peripheral compartment of the fetus, and the lag time necessary for plasma-brain equilibration explains the lack of correlation between the incidence of respiratory depression and fetal plasma drug concentration.

The Distribution of Drugs into Amniotic Fluid and Allantoic Fluid

The widespread use of amniotic fluid as a means for monitoring fetal status, and the potential development of intra-amniotic drug infusion as a route of fetal drug administration, has led to an increasing interest in the dynamics of drug movement between mother, fetus, and amniotic fluid. The fetal lamb differs from the human fetus in that it is not only surrounded by the amniotic sac, but also by the allantoic sac. The anatomy of the fetal lamb and the fluid sacs is shown in Figure 4. In the third trimester, the major contribution of fluid into the amniotic sac and allantoic sac is fetal urine. Fetal urine is excreted into the amniotic sac via the urethra, and into the allantoic sac via the urachus. Fluid balance is maintained in these fluid sacs by continuous fetal swallowing and reabsorption of fluid across the respiratory tract and the chorio-allantoic membrane. The fluid dynamics in the human maternal-fetal unit was recently reviewed by Seeds (64, 65) and in the ovine maternal-fetal unit by Mellor & Slater (66) and Barnes (67).

There is experimental evidence that many drugs administered to the pregnant ewe are found in amniotic fluid. These include sodium salicylate

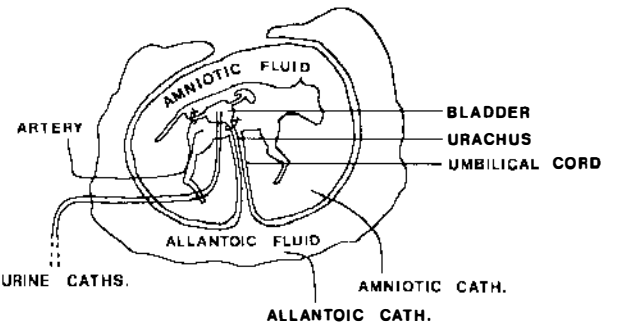

Figure 4 A schematic representation of the relationship of the fetal lamb urinary bladder to the amniotic sac and allantoic sac [from Szeto et al (42) with permission].

(46), mannitol (43), meperidine (37), lidocaine (45), and methadone (H. H. Szeto et al, unpublished data). The appearance of drug in amniotic fluid is usually delayed following a single intravenous dose to the mother, but the concentration in amniotic fluid gradually increases, and peak concentration usually far exceeds the concurrent concentrations in maternal and fetal plasma. The delay in appearance of drug in amniotic fluid, and the subsequent accumulation of drug in amniotic fluid suggest that the major source of drug comes from fetal urine. There is now good evidence that mannitol (43), meperidine (37), and methadone (H. H. Szeto et al, unpublished data) are all excreted by the fetus into urine. Fetal urine, however, may not be the only source since it has been found that even if the urethra and urachus were both ligated, meperidine can still be detected in amniotic fluid and allantoic fluid (42). The time-course of meperidine concentration in the two fluid sacs actually suggests that meperidine first diffuses across the chorio-allantoic membrane into the allantoic sac, and then diffuses across the allantoic and amniotic membranes into the amniotic sac.

The accumulation of drugs in amniotic fluid indicates that equilibration of these compounds with the fetus is very slow. Basic drugs may accumulate in amniotic fluid because of a trapping effect due to the lower pH of amniotic fluid as compared to fetal plasma (37). When meperidine was administered directly into the amniotic sac, there was rapid appearance of meperidine in maternal plasma followed by a slower appearance in fetal plasma (37). Thus, it appears that diffusion across the chorio-allantoic membrane is the predominant pathway for meperidine in amniotic fluid. This provides the final route of drug elimination from the fetal compartment.

Based on the information obtained from these various studies, we can propose a pharmacokinetic model for the maternal-fetal unit that would include the fluid sacs (see Model 4, Figure 5). Following maternal drug administration, the drug may be distributed to the fetus via the umbilical vein, and it may diffuse across the chorio-allantoic membrane into the allantoic sac. In the fetus, some drugs may be excreted into urine, and

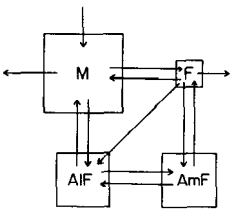

Figure 5 A four-compartment open model describing the disposition of a drug in the mother (M), fetus (F), amniotic sac (AmF), and allantoic sac (AlF).

appear in amniotic fluid and allantoic fluid. There is free exchange of drugs between the two fluid compartments. There does not appear to be direct exchange between the amniotic fluid compartment and the maternal compartment; but from the allantoic fluid compartment, drugs may diffuse back to the maternal compartment across the chorio-allantoic membrane.

THE EXTENT OF FETAL DRUG EXPOSURE

To compare the relative safety of different drugs for the developing fetus, it is necessary to have an index for quantitating the extent of fetal exposure following drug administration to the mother. The selection of an index of relative fetal exposure depends on the mechanism of action of the drug of interest, and the duration of drug exposure.

For drugs which produce irreversible effects in the fetus, such as teratogenicity, it is thought that the intensity of response is directly proportional to the total number of receptors interacting with the drug molecules (68). It is, therefore, the integral of drug concentration over time which is the essential pharmacokinetic determinant of the intensity of response (68). Levy & Hayton (29), therefore, suggested that the ratio of the total area under the drug concentration versus time curve of the fetus to that of the mother may serve as an index of relative exposure of the fetus to a drug administered to the mother. If such a drug is administered to the mother repeatedly for a prolonged period of time, a steady state will eventually be reached in the mother and fetus, and the ratio of the steady state drug concentration in the fetus to that in the mother may be used as the index of relative drug exposure.

For reversibly-acting drugs, the intensity of pharmacologic effect is directly related to drug concentration in plasma (69), and it would, therefore, be appropriate to compare the ratio of peak drug concentration in the fetus to that in the mother. If the drug is given chronically throughout pregnancy, the ratio of fetal steady state drug concentration to maternal steady state drug concentration should be used.

FACTORS WHICH DETERMINE DRUG DISTRIBUTION BETWEEN MOTHER AND FETUS

As demonstrated earlier, the distribution of a drug between mother and fetus at steady state is determined not only by the binding of the drug in maternal and fetal plasma, but also by the bidirectional clearances of the drug across the placenta, and clearance of the drug by nonplacental routes from the fetal compartment (see equation 6).

Plasma Protein Binding

The binding of drugs to maternal and fetal plasma proteins is not well understood. While some drugs appear to bind to the same extent in maternal and fetal plasma, such as phenytoin (32), indomethacin (34), and acetylsalicylic acid (31), others have been found to bind to a lower extent in fetal plasma, including dexamethasone (33), salicylate, (46) and meperidine (37). Much of the variation in these studies may be due to the varying gestational ages of the animals used in the studies. Recently, it was found that the extent of methadone binding in fetal plasma changes significantly with gestational age of the fetus (38b). The extent of fetal binding was initially much lower than maternal binding, but increased significantly in the last two weeks of gestation, reaching the level of maternal binding by the time of birth (38b). Moreover, we found that the time at which the increase begins may vary considerably between animals. Thus there may be a large interindividual variation in fetal binding near term, and this should be considered when evaluating maternal and fetal drug concentrations.

Placental Drug Clearance

The rate of diffusion of a drug across the placenta is determined by the physicochemical properties of the drug and the physiologic characteristics of the maternal-fetal unit. This was clearly demonstrated in the comparison of placental clearance of morphine and methadone in the pregnant ewe (38a). The difference between the apparent partition coefficient (52) of morphine (1.42) and methadone (116.33) can easily account for the 15-fold difference in the clearance from the maternal to the fetal compartment. The diffusibility of some lipid-soluble compounds across the placenta may be so high that their clearances will be limited by the rate of blood flow to the placenta. Thus changes in uterine and umbilical blood flow may affect the placental clearance of some drugs. Decrease in uterine blood flow following the maternal administration of epinephrine has been shown to decrease placental clearance of antipyrine (70). At the same time, the placental clearance of urea, a diffusion-limited compound, was not affected. Differences in uterine and umbilical blood flows may, in part, account for the large interindividual variation observed in the placental clearance of methadone; variation between animals is significantly less for morphine, which is a much more polar compound and its placental clearance is probably diffusion-limited (38a). It is therefore important that studies on placental drug clearance be conducted on an unanesthetized animal that is not under stress.

Fetal Drug Clearance

As mentioned in the preceding pharmacokinetic discussions, fetal plasma drug concentration will always approach maternal drug concentration at steady state unless the drug was eliminated by the fetus. Therefore, in the case of chronic drug exposure throughout pregnancy, fetal drug clearance will be the most important factor to consider. However, in the case of acute drug exposure during labor, we are more concerned with the drug concentration in the fetus at the time of delivery, and both placental clearance and fetal clearance will be important considerations.

Our current knowledge on fetal drug elimination *in utero* is rather limited. Renal clearance has been determined for meperidine (42, 44), lidocaine (45), and methadone (H. H. Szeto et al., unpublished data). Fetal drug elimination by biotransformation has for the most part only been studied using in vitro enzyme preparations. It is not known how closely the activities of the enzymes, as measured in vitro, reflect their in vivo activities. The pharmacokinetic approach presented in this chapter provides an opportunity for quantitating total fetal drug clearance due to biotransformation. Biotransformation clearance will simply be total nonplacental clearance of the drug from the fetal compartment minus renal clearance.

As the extent of fetal drug clearance increases throughout pregnancy, the distribution of a drug between mother and fetus will change. The contribution of fetal drug clearance to the overall clearance of methadone from the fetal compartment has been found to increase throughout the third trimester until two weeks prior to birth in the fetal lamb, while it remained constant for morphine during the last four weeks of gestation (38a). This difference may reflect the different biotransformation pathways for the two drugs. In the adult, methadone is *N*-demethylated while morphine is conjugated and excreted as its glucuronide. These findings would suggest that the rate of development of the *N*-demethylase enzyme system is different from that of the Phase II conjugation system.

CONCLUSIONS

This review has considered some of the factors that are important in determining the extent of fetal exposure to maternally-administered drugs by means of pharmacokinetic modeling of the maternal-fetal unit. Attempts have been made to support and validate the proposed models with experimental data that have been obtained using the pregnant ewe model. Current data suggest that fetal drug clearance as well as placental drug clearance plays a very important role in determining the extent of fetal drug exposure.

The chronic pregnant ewe model has been demonstrated to be a particu-

larly useful animal model for the study of maternal-fetal pharmacokinetics. A knowledge of drug pharmacokinetics in the maternal-fetal unit will provide a rational basis for the selection of drugs and the design of safer and more effective dosage regimens during pregnancy.

Recently, the increasing ability to diagnose fetal disease has introduced the idea of treating the fetus *in utero* by administration of the drug to the mother, into the amniotic sac, or even directly into the fetus. Information on maternal-fetal-amniotic fluid pharmacokinetics is urgently needed to aid in the selection of an appropriate route of administration and dosage regimen for the fetus.

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