# *Binding of Anilide-type Local Anesthetics in Human Plasma:*

## *II. Implications* In Vivo, *with Special Reference to Transplacental Distribution*

*Geoffrey T. Tucker, Ph.D.,* Robert N. Boyes, Ph.D.,† Phillip O. Bridenbaugh, M.D.,‡ Daniel C. Moore, M.D.‡*

Using an ultrafiltration technique, significantly less bupivacaine and lidocaine have been shown to bind, *in vitro*, in human umbilical plasma than in corresponding maternal plasma. Competitive binding of the agents and the absence of significant binding in cerebrospinal fluid have also been demonstrated. Umbilical/maternal bupivacaine concentration ratios at delivery in blood samples from women receiving the drug for caudal or epidural block were significantly lower than corresponding ratios reported in the literature for lidocaine and mepivacaine (0.2–0.4 *vs.* 0.5–0.7). Differences between the plasma binding of bupivacaine, lidocaine and mepivacaine may explain, in part, observed differences between their placental passage. (Key words: Bupivacaine; Mepivacaine; Lidocaine; Plasma binding; Placental transfer; Drug interaction; Caudal and epidural block.)

In a companion paper,[1] the rank-order of binding in human plasma for a series of anilide-type local anesthetics, determined using ultrafiltration and gas chromatography techniques, was reported as: bupivacaine (Marcaine) > mepivacaine (Carbocaine) > lidocaine (Xylocaine) > the N-dimethyl analog of lidocaine. These data have been supplemented by an investigation of the possibilities of competitive binding of the drugs, binding in cerebrospinal fluid, and differential binding in maternal and umbilical plasma. Implications of the binding properties of the agents are discussed with reference to their distribution, elimination and placental transfer.

## Methods

### Ultrafiltration

The following experiments were performed using the previously described ultrafiltration procedure [1]:

1) Plasma-binding of lidocaine and bupivacaine, when present together, was compared with that observed when the drugs were added singly to plasma. Pooled plasma from six subjects was used; the experiment was carried out in duplicate. The total plasma concentration of each drug was 5 μg/ml.

2) Binding of bupivacaine and lidocaine at the 5 μg/ml level was determined in normal cerebrospinal fluid pooled from six subjects. Experiments with each drug were carried out in duplicate.

3) Samples of maternal and umbilical venous blood were obtained from women at delivery under general anesthesia. The binding (at the 1 and 5 μg/ml levels) of bupivacaine and the binding of lidocaine in corresponding maternal and umbilical plasmas were compared.

### Determination of Bupivacaine in Maternal and Umbilical Blood and Plasma at Delivery

Subjects of the studies were two groups of *primigravidae* to whom bupivacaine was administered for caudal or epidural block during labor. Most patients received a standard premedication of meperidine (50 mg) and pro-

* Research Investigator in Anesthesiology, Virginia Mason Research Center, Seattle, Washington 98101.

† Head, Drug Disposition Section, Astra Pharmaceutical Products, Inc., Worcester, Massachusetts 01606.

‡ Staff Anesthesiologist, The Mason Clinic, Seattle, Washington 98101.

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TABLE 1. Results of Ultrafiltration Experiments

| | Experiment: Per cent Binding | | | | |
|---|---|---|---|---|---|
| | Competition* (Plasma Pools from Six Subjects) | | Cerebrospinal Fluid (Pools from Six Subjects) | Maternal/Fetal† | |
| | Single Drug | Combination (lid. + bup.) | | Maternal Plasma | Fetal Plasma |
| Bupivacaine | | | | 88.9 | 55.8 |
| | | | | 84.1 | 48.8 |
| 5 μg/ml | 84.2 | 77.6 | Not significant | 86.1 | 53.4 |
| | 89.0 | 82.4 | Not significant | 93.0 | 47.7 |
| 1 μg/ml | | | | 96.8 | 66.5 |
| | | | | 94.0 | 63.0 |
| | | | | 95.2 | 67.1 |
| Lidocaine | | | | 49.0 | 7.1 |
| 5 μg/ml | | | | 40.7 | 24.4 |
| | 51.0 | 29.5 | Not significant | 45.6 | 10.9 |
| | 56.2 | 27.7 | Not significant | 45.7 | 12.9 |
| 1 μg/ml | | | | 53.2 | 21.4 |
| | | | | 58.1 | 24.2 |
| | | | | 57.6 | 27.0 |

* Differences between binding in single drug and combination were only significant at $P < 0.2$ (bupivacaine data), and $P < 0.01$ (lidocaine data).
† Differences between maternal and fetal binding were significant for both drugs at $P < 0.001$.

methazine (25 mg). As a rule, no further analgesic was required after inception of the block.

*Group I:* Five patients were studied during vaginal delivery and one during cesarean section/hysterectomy. Bupivacaine hydrochloride was given in 0.5 per cent concentration without epinephrine, the total dosage varying from 135 to 260 mg. Two patients received two doses each (see table 2). Bupivacaine concentrations at delivery were determined in whole blood taken from a maternal antecubital vein and from the umbilical vein and artery. In each of four cases a simultaneous sample from a maternal brachial artery was also analyzed. The ratios of drug concentration in umbilical vein to the corresponding concentrations in both maternal vein and umbilical artery were calculated.

*Group II:* Six patients were studied during vaginal delivery. Bupivacaine hydrochloride was given in 0.25 per cent concentration with or without epinephrine, the total dosage varying from 35 to 155 mg. Two patients received more than one dose each (see table 3). Bupivacaine concentrations at delivery were determined in whole blood and plasma from a maternal antecubital vein and from the umbilical vein. Hematocrits were measured using a microtechnique. The ratio of drug concentration in the umbilical vein to that in a maternal vein was calculated. Also, the percentages of drug in whole blood confined to plasma were determined in both maternal and umbilical samples.

## Results

### ULTRAFILTRATION

The results, summarized in table 1, indicate that the binding of bupivacaine and the binding of lidocaine were reduced by approximately 7 per cent and 25 per cent, respectively, when these drugs were present concurrently in plasma at the same total concentrations.

Data in table 1 also indicate that, on the average, 88 per cent bupivacaine and 45 per cent lidocaine were bound in maternal plasma,

TABLE 2. Distribution of Bupivacaine in Maternal and Umbilical Whole Blood at Delivery: Data for Group I

| | Age (years) | Route | Bupivacaine Dose (mg) | Time (min) | Time to Delivery (min) | Bupivacaine Concentration (μg/ml) | | | $\frac{C_{uvb}}{C_{mb}}$ | $\frac{C_{uab}}{C_{uvb}}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Maternal Venous Blood ($C_{mb}$) | Umbilical Venous Blood ($C_{uvb}$)† | Umbilical Arterial Blood ($C_{uab}$)‡ | | |
| Patient 1 | 21 | Caudal | I. 125 | 0 | 210 | 0.70 (0.72*) | 0.19 | 0.16 | 0.27 | 0.84 |
| | | | II. 125 | 149 | | | | | | |
| Patient 2 | 23 | Caudal | I. 135 | 0 | 215 | 0.80 (0.83*) | 0.24 | 0.17 | 0.33 | 0.71 |
| | | | II. 125 | 145 | | | | | | |
| Patient 3 | 22 | Caudal | 135 | 0 | 102 | 0.51 (0.51*) | 0.08 | 0.06 | 0.64 | 0.75 |
| Patient 4 | 30 | Caudal | 150 | 0 | 93 | 0.25 | 0.07 | 0.07 | 0.36 | 1.00 |
| Patient 5 | 28 | Caudal | 150 | 0 | 197 | 0.22 (0.23*) | 0.06 | 0.06 | 0.28 | 0.75 |
| Patient 6 | 35 | Caudal | 150 | 0 | 55 | 0.49 | 0.15 | 0.13 | 0.33 | 0.87 |
| MEAN ±SD | | | | | | | | | 0.37 ±0.14 | 0.82 ±0.11 |

* Simultaneous arterial level.
† Difference between data in columns 7 and 8 significant at $P < 0.001$.
‡ Difference between data in columns 8 and 9 only significant at $P < 0.2$.

compared with only 51 per cent and 14 per cent, respectively, in umbilical plasma at the 5 μg/ml level. Corresponding figures at the 1 μg/ml level were 95 per cent and 56 per cent, compared with 66 per cent and 24 per cent. There were no marked differences between the binding data for plasma taken from women in labor and those for plasma taken from men and nonpregnant women (mean percentage binding at the 5 μg/ml level was 85 per cent for bupivacaine; it was 51 per cent for lidocaine).[1]

Significant binding of lidocaine and bupivacaine in cerebrospinal fluid was not observed.

TABLE 3. Distribution of Bupivacaine in Maternal and Umbilical

| | Age (years) | Route | Epinephrine 1:200,000 | Bupivacaine Dose (mg) | Time (min) | Time to Delivery (min) | Bupivacaine (μg/ml) | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Maternal Venous Blood ($C_{mb}$)* | Maternal Venous Plasma ($C_{mp}$) |
| Patient 7 | 23 | Epidural | Yes | I. 30 | 0 | 170 | 0.29 | 0.49 |
| | | | | II. 30 | 160 | | | |
| Patient 8 | 22 | Epidural | No | 35 | 0 | 30 | 0.34 | 0.60 |
| Patient 9 | 28 | Caudal | Yes | 65 | 0 | 96 | 0.17 | 0.29 |
| Patient 10 | 25 | Caudal | No | 48 | 0 | 40 | 0.35 | 0.56 |
| Patient 11 | 28 | Caudal | No | I. 55 | 0 | 215 | 0.37 | 0.61 |
| | | | | II. 50 | 95 | | | |
| | | | | III. 50 | 190 | | | |
| Patient 12 | 21 | Caudal | Yes | 53 | 0 | 104 | 0.11 | 0.20 |
| MEAN ±SD | | | | | | | | |

* Difference between data in columns 8 and 10 (also 9 and 11) significant at $P < 0.001$.
† Difference between data in columns 16 and 17 significant at $P < 0.001$.

### Transplacental Distribution of Bupivacaine

Data are summarized in tables 2 and 3. Maternal complications were not many or severe, and the infants were vigorous at delivery.

The ratio of the concentration of drug in umbilical venous blood to that in corresponding maternal venous blood was significantly higher for Group I subjects (mean 0.37) than for Group II subjects (mean 0.21) ($P < 0.001$).

Analysis of peripheral venous whole blood, sampled frequently from Group I patients prior to delivery, indicated that peak maternal levels fell in the range of 0.5 to 0.9 μg/ml and occurred between 15 to 30 minutes after dosage. Peripheral arterial whole blood samples showed consistently higher levels of bupivacaine than peripheral venous samples. An arteriovenous difference, of the order of 20 to 40 per cent at its maximum, persisted for as long as about an hour after administration. This observation and analysis of arterial blood samples from four of the patients at delivery demonstrated that in Group I subjects there was very little difference between maternal arterial and venous drug levels at the time of birth. In four of the patients in Group II, however, it is possible that maternal arterial levels were somewhat higher than the measured maternal venous levels at delivery.

At delivery, the concentration of bupivacaine in the umbilical artery was about 20 per cent lower than that in the umbilical vein (Group I study). Also, about 25 per cent of the total drug in umbilical whole blood was found to be associated with the erythrocytes, in contrast to the almost complete confinement of the drug to the plasma in maternal blood (Group II study).

## Discussion

### In Vivo Implications of the Plasma-binding of Local Anesthetics

*Relative Distribution and Elimination:* With the aid of simple models of the form shown in figure 1, it is possible to make certain predictions from the data reported in parts I and II of this communication concerning the relative distribution and elimination of local anesthetic agents. Obviously, some of these predictions will be more speculative than others, depending upon the availability of experimental data relating to other variables, apart from plasma-binding, that may influence disposition of the drugs.

In model *a*, figure 1, free drug in plasma

Whole Blood and Plasma at Delivery: Data for Group II

| concentration | | | | | | | |
|---|---|---|---|---|---|---|---|
| Umbilical Venous Blood ($C_{ub}$) | Umbilical Venous Plasma ($C_{up}$) | $\frac{C_{ub}}{C_{mb}}$ | $\frac{C_{up}}{C_{mp}}$ | Maternal Hematocrit (Per Cent) | Umbilical Hematocrit (Per Cent) | Per Cent Total Drug in Maternal Plasma† | Per Cent Total Drug in Umbilical Plasma |
| 0.06 | 0.09 | 0.21 | 0.18 | 43 | 50 | 96.3 | 75.0 |
| 0.06 | 0.08 | 0.18 | 0.13 | 43 | 58 | 100.6 | 56.0 |
| 0.05 | 0.09 | 0.29 | 0.31 | 43 | 60 | 97.2 | 72.0 |
| 0.05 | 0.07 | 0.20 | 0.13 | 37 | 47 | 100.8 | 74.2 |
| 0.08 | 0.16 | 0.22 | 0.26 | 40 | 51 | 98.9 | 98.0 |
| 0.02 | 0.04 | 0.18 | 0.20 | 43 | 57 | 103.6 | 79.5 |
| | | 0.21 ±0.04 | 0.20 ±0.08 | | | 99.6 ±2.7 | 75.8 ±20.0 |

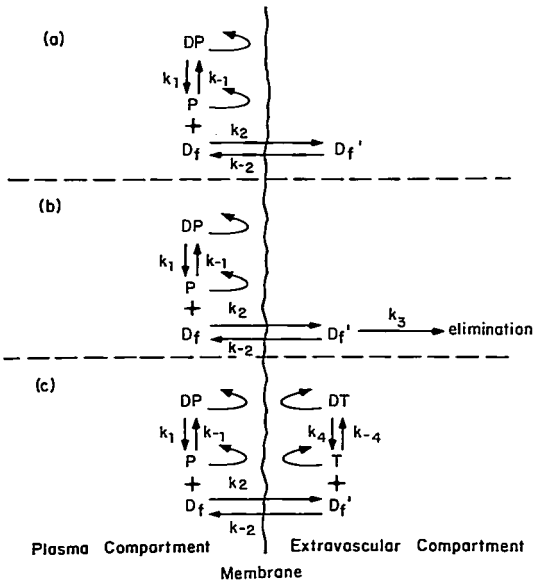


FIG. 1. Simple models representing the *in vivo* distribution of a plasma-bound drug between plasma and extravascular compartments. (Where: DP = drug–plasma complex; P = plasma-binding component; $D_f$ = drug free in plasma; $D_f'$ = drug free in extravascular compartment (for partially ionized drugs, concentration of $D_f'$ may differ from that of $D_f$ owing to a *p*H differential between plasma and extravascular compartment); DT = drug–tissue complex; T = tissue-binding component; k's represent rate constants. Only free drug is assumed to cross the biological membrane.)

is in equilibrium with bound drug in plasma and free drug in an extravascular compartment separated by a semipermeable membrane. Binding is assumed to be freely reversible. Clearly, plasma-binding of the drug will limit its distribution into the extravascular compartment if only free drug is allowed to cross the membrane. At equilibrium the amount transferred will also depend upon the relative volumes of the plasma and extravascular compartments. In the approach to equilibrium, the net rate of drug transfer will depend upon the relative values of the rate constants involved in the scheme. Substances that are very lipid-soluble will tend to equilibrate at net rates limited only by blood flow to the exchanging surface. For drugs transferred at moderate or slow rates, however, diffusion across the membrane will tend to become rate-limiting, and plasma binding can then also influence the rate of equilibration.[2] Model *a* may be used to represent, for example, the distribution of many drugs between plasma and cerebrospinal fluid.

On the basis of our plasma-binding data,[1] therefore, we could predict, for example, that since no significant binding of the local anesthetics was observed in cerebrospinal fluid (see table 1), proportionately, much less bupivacaine than lidocaine or mepivacaine would be able to enter the cerebrospinal fluid *in vivo*. Conversely, bupivacaine injected into the cerebrospinal fluid might leave this compartment and enter the plasma more rapidly than lidocaine or mepivacaine. The possibility of differential binding to spinal cord and brain tissue, and the relative $pK_a$ and lipid-solubility values [1] of the agents, would tend to complicate the issue, however.

In the situation represented by model *b*, figure 1, the rate constant, $k_3$, refers to a process causing removal of free drug from the extravascular compartment without removal of a corresponding volume of water. Equi-

librium is upset, and more free drug is continually produced by dissociation of the plasma–drug complex. In the extreme case, where the transfer processes are rapid compared with the rate of passage of blood through the capillaries of the region concerned, complete removal of drug from plasma carried into the region may be possible. Plasma binding will not inhibit drug disposition under these circumstances. This situation is most closely approached when active elimination processes such as drug metabolism in the liver and secretion at the renal tubules are involved. Extensive plasma binding may even enhance the metabolism of a drug by ensuring the delivery of larger amounts to the liver as a consequence of reduced passive removal of drug from the plasma elsewhere in the body.[3]

In common with other basic drugs, the anilide-type local anesthetics are concentrated extravascularly, to a large extent. Clearly, therefore, plasma binding does not inhibit the overall distribution and elimination of these drugs significantly. In fact, in the series, bupivacaine, mepivacaine, lidocaine, the first compound appears to be most rapidly eliminated from the blood,[4] despite its more extensive plasma binding.

The situation depicted by model *c*, figure 1, is intermediate between those represented by models *a* and *b*. In this case, binding occurs in the extravascular compartment, where DT represents a complex between drug and a "tissue" component. Diffusion of drug from plasma into compartments containing binding sites which accept it more avidly than plasma sites will tend not to be limited by plasma binding, whereas that to a compartment with fewer binding sites or sites with less affinity may be reduced. A solubilization process in the extravascular compartment would produce effects similar to those of a tissue-binding process.

The distribution of local anesthetics between plasma and erythrocytes may be described by a scheme analogous to that defined by model *c*. In this case, plasma binding lim-

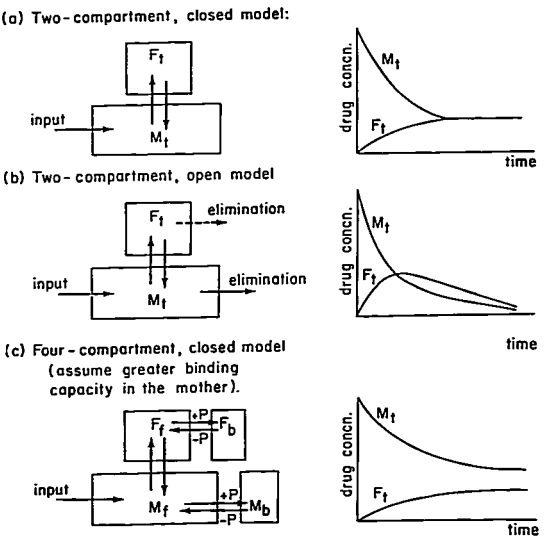


FIG. 2. Simple compartmental models illustrating maternal–fetal drug distribution. (F = drug in fetus; M = drug in mother; subscripts t, f and b refer to total, free and bound drug, respectively. Curves were drawn freehand and serve only to indicate general trend of distribution). A detailed discussion of compartmental models of the above form may be found, for example, in references 16 and 17).

its access and binding to erythrocyte components.[1] In the following discussion, we will attempt to show how a model similar to model *c* may also be used to explain, at least in part, the placental transfer of the local anesthetics.

*Placental Transfer:* Despite the greater lipid solubility of bupivacaine compared with lidocaine and mepivacaine,[1] umbilical/maternal bupivacaine ratios found in the clinical studies (see tables 2 and 3) were lower than corresponding ratios reported in the literature for the latter drugs. Our general observation of ratios of the order 0.2 to 0.4 for bupivacaine is consistent with the findings of Reynolds and Taylor,[5] and contrasts with umbilical/maternal concentration ratios for lidocaine and mepivacaine which have been reported to fall predominantly in the range 0.5 to 0.7.* [5-15, 30, 31] The ratio for prilocaine (Citanest) is about 1.0.[11, 21] In strictly relative terms it is possible, therefore, that the risk of fetal intoxication following administration of bupivacaine to the mother may be reduced compared with that following administration of other anilide-type agents.

In order to attempt an explanation of the above differences some understanding of the kinetics of maternal–fetal drug distribution is necessary. Thus, in figures 2*a* and *b* we have represented the biological system in terms of the simplest compartmental model. Here, the mother and fetus are represented by a two-compartmental system in which the respective body compartments are considered homogeneous. Assuming that no elimination occurs, *i.e.*, the model is closed, after an intravenous injection of drug into the mother, maternal and fetal drug levels will approach each other and become identical when a state of equilibrium is attained (figure 2*a*). If, however, the maternal blood level is falling sufficiently rapidly as a result of elimination, *i.e.*, the model is open, it is theoretically possible for the fetal drug level to exceed the maternal level, then for net placental transfer to proceed from fetus to mother[2] (figure 2*b*). If this occurs, the concentration of drug in the umbilical artery would be expected to exceed that in the umbilical vein.

Plasma-binding will further complicate the issue. As a gross approximation, the distribution of a drug between maternal intervillous plasma and fetal intravillous plasma may be considered a special example of the situation represented by model *c* in figure 1. Plasma-binding sites, in this instance, are present on both sides of the membrane, *i.e.*, placenta. Although the placenta will permit very slow passage of proteins,[18, 19] the time scale of drug distribution is usually such that it essentially constitutes a barrier to the passage of drugs bound to macromolecules. For those drugs which are transferred at rates either completely or partially controlled by diffusion, therefore, plasma binding can potentially have a delaying effect.[2] Furthermore, if for some reason fetal plasma is incapable of binding as much drug as maternal plasma, then the total concentration of drug in the former will be lower than that in the latter, even under the ideal condition of a state of equilibrium (see figure 2c).

In general, therefore, the plasma-binding data for bupivacaine, mepivacaine and lidocaine are consistent with the relative umbilical /maternal ratios observed for the drugs. Thus, the more extensive binding of bupivacaine might be expected to delay passage across the placenta, compared with lidocaine and mepivacaine. Calculations (see Appendix) suggest, however, that the observed fetal–maternal drug gradients may result largely from the lower binding of the drugs in umbilical plasma compared with maternal plasma (see table 1), rather than from an effect of plasma binding on the *rate* of equilibration. Less extensive binding of the agents in umbilical plasma, compared with maternal plasma, reflects a reduction in the concentration of binding macromolecules, in the number of binding sites per macromolecule, or in the association constant for the drug–macromolecule complex. Alternatively, the above variables may not be different, and higher levels of endogenous compounds capable of displacing the drugs from binding sites may be present in umbilical plasma. (It should be pointed out that our results are not in accord

* It should be pointed out that this range is based on values obtained using both gas chromatographic and relatively nonspecific dye-complexing methods of analysis, and measurements of maternal arterial or venous plasma or whole blood.

with those of Shnider and Way,[6] who observed no difference between binding of lidocaine in umbilical and in maternal plasma.) If it is assumed that the binding of drug in plasma prevents its association with erythrocytes,[1] then findings from the transplacental distribution study, in which plasma/whole blood drug concentration ratios were compared in mother and infant (see table 3), support our ultrafiltration data. Thus, more bupivacaine was associated with erythrocytes in umbilical blood than in maternal blood.

Observation of a trend toward higher levels of bupivacaine in the umbilical vein compared with those in the umbilical artery, sampled simultaneously (see table 2), suggests that net placental transfer of the drug generally proceeds from mother to fetus. This also seems to be the case after administration of lidocaine and mepivacaine when, with a few exceptions,† concentration ratios of drug in umbilical artery to drug in umbilical vein similar to those observed for bupivacaine have been reported.[6, 9, 10, 13] Even when lidocaine was administered by rapid intravenous injection, the level of drug in the umbilical artery did not exceed the level in umbilical vein.[6] That local anesthetics are capable of passing rapidly from fetus to mother is indicated by the studies of Morishima and Adamsons,[20] who injected mepivacaine directly into guinea pig fetuses *in utero*. In contrast to findings with lidocaine, mepivacaine and bupivacaine, data obtained from a study involving epidural administration of prilocaine suggested that net reverse transfer of this drug occurs about 50 minutes after administration, as evidenced by concentration ratios of drug in umbilical artery to drug in umbilical vein greater than unity.[21] umbilical levels of prilocaine slightly in excess of corresponding maternal levels have also been reported, although differences were not significant.[11, 21] That prilocaine is less extensively bound in plasma than lidocaine [22] (and, therefore, less bound than mepivacaine and bupivacaine [1]) may help to explain these findings.

† In five of 12 infants found to be depressed at birth, Morishima *et al.*[18] observed that the difference between mepivacaine concentrations in umbilical vein and artery were small or reversed.

A further consideration in the interpretation of umbilical/maternal blood drug levels is the form of the maternal input function. Thus, placental transfer may depend upon drug dosage and concentration and the rate and route of administration, inasmuch as these factors will determine maternal plasma drug levels. If it is assumed that drug disposition may be described in terms of simple kinetic models in which distribution and elimination are represented as apparent first-order processes, then dose, rate, and route of drug administration will not affect the relative amount of drug ultimately transferred to the fetus. This situation is implicit in models *a* and *b* in figure 2. Dose, rate and route of administration might be expected to have significant effects on the amount of drug transferred only if the kinetics of drug disposition are nonlinear, for example, if a plasma- or tissue-binding process is involved or drug metabolism or excretion processes tend to become saturated.‡ For those drugs bound in plasma, the proportion of free drug will be less at lower total plasma drug concentrations.[2] Therefore, plasma binding will tend to produce a dependence of placental drug transfer on dose, rate and route of drug administration.

Conceivably, the higher umbilical/maternal bupivacaine ratios in Group I subjects compared with those in Group II subjects may be related, via a nonlinear distribution process (such as plasma binding), to the greater dosage and/or concentration of drug used in the former group.

*Competition for Binding.* Although the clinical use of mixtures of anilide-type agents is not common, some anesthesiologists may substitute one agent for another during continuous epidural block in an attempt to offset

‡ Crawford [23, 24] agrees that, in a closed system, the same proportion of drug will be passed from mother to fetus irrespective of the method of administration. He suggests, however, that in an open system, when the drug enters the maternal circulation in very dilute form or very slowly (*e.g.*, following slow iv infusion or im injection), "... the attrition of the maternal supply of drug by the processes of metabolism and excretion will diminish considerably the total amount which is finally able to make its way across the placenta," compared with that which passes across after rapid iv injection. The general validity of this argument appears to depend on the nature of the kinetics of drug metabolism and excretion.

the development of tachyphylaxis. More commonly, mixtures of an anilide-type agent (lidocaine or mepivacaine) with tetracaine (Pontocaine), an ester-type agent, are employed in order to take advantage of the rapid onset of the former and the prolonged duration of the latter.[26, 27] Therefore, competition between the agents for plasma-binding sites (table 1) or tissue-binding sites may affect the course of drug disposition and incidence of toxic reactions. Similarly, coadministration of other drugs reacting with common binding sites may also have clinical implications.[28] Gillette[29] has indicated, however, that such displacement reactions should be interpreted with caution.

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## Appendix

### *Calculation of Theoretical Umbilical/Maternal Plasma Drug Concentration Ratios from Plasma-binding Data*

If we (naïvely) assume a simple model for transplacental drug distribution of the form of model *c* in figure 1, the relationship between the plasma-binding data and observed umbilical/maternal drug ratios may be investigated in a more quantitative manner. In order to do this, however, it is first necessary to establish several assumptions. These include:

1) The placental interface functions as a simple, inert, semipermeable membrane with respect to transfer of the local anesthetics, *i.e.*, transfer proceeds by passive diffusion of unbound drug. There is no evidence to suggest either way that other processes involving active transport, facilitated diffusion, "solvent drag" effects, membrane charges, etc., may be important or not in the case of these drugs.

2) Plasma binding determined *in vitro* is the same as *in vivo* (intravascular) binding. (*N.b.*, All binding data were determined at 25 C and not at body temperature.)

3) Plasma drug levels and binding in umbilical and peripheral maternal blood vessels accurately reflect the situation on respective sides of the placental "barrier." (Homogeneous blood samples are difficult to obtain from the intervillous space and blood from the intravillous space cannot be sampled readily.[c])

4) Distribution and redistribution of local anesthetic within the tissue mass of the placenta does not rate-limit the equilibration of drug between maternal and fetal plasma.

5) The local anesthetics are not metabolized by placental enzyme systems. (Shnider and Way [6] have shown that lidocaine is not metabolized by homogenates of human placental tissue.)

If the above assumptions are valid, it should be possible to predict *equilibrium* umbilical /maternal plasma drug ratios (R) from relative plasma-binding data. The necessary calculations may be carried out as follows:

1) Let total drug concentration in umbilical plasma = $C_{up}$ [We took values of 0.1, 1 and 5 $\mu$g/ml. This range covers experimental values of $C_{up}$ reported in the literature for lidocaine [5-11]; corresponding values for bupivacaine are generally of the order 0.1 $\mu$g/ml and below (see tables 2 and 3 and reference 5)].

2) The percentage drug binding at $C_{up}$ is taken from data in table 1 (binding at $C_{up}$ = 0.1 $\mu$g/ml was estimated by extrapolation).

3) Therefore, the concentrations of free drug in umbilical plasma ($C_{upf}$) may be estimated for various values of $C_{up}$.

4. Assume equilibrium distribution of free drug between maternal and umbilical plasma, *i.e.* $C_{upf} = C_{mpf}$ (free drug concentration in maternal plasma).

5) Determine total maternal drug concentrations ($C_{mp}$) at which free drug concentrations are $C_{mpf}$. Approximate values can be obtained by extrapolation of data in table 1 and from previously reported binding *vs.* concentration data.[1]

6) If $C_{mp}$ and $C_{up}$ can be estimated, then the theoretical distribution of drug between maternal and fetal plasma at equilibrium, $R = C_{up}/C_{mp}$, can be calculated and compared with experimental values.

TABLE 4. Theoretical Equilibrium Umbilical/Maternal Drug Concentration Ratios (R) Calculated Using Plasma-binding Data*

| | Lidocaine | | | Bupivacaine | | |
|---|---|---|---|---|---|---|
| Total drug concentration in umbilical plasma ($C_{up}$, μg/ml) | 5 | 1 | 0.1 | 5 | 1 | 0.1 |
| R (assuming no *p*H difference between maternal and fetal plasma) | 0.7 | 0.6 | 0.5 | 0.5 | 0.3 | 0.1 |
| R (assuming maternal plasma *p*H, 7.4; fetal plasma *p*H, 7.2) | 0.9 | 0.8 | 0.7 | 0.6 | 0.3 | 0.2 |

* As explained in the text, experimental R values for lidocaine are mostly of the order 0.5–0.7 ($C_{up}$ = 0.1–5 μg/ml) and for bupivacaine of the order 0.2–0.4 ($C_{up} \simeq 0.1$ μg/ml).

Theoretical R values obtained in this manner are shown in table 4 (mean values of percentage binding at each $C_{up}$ value were taken or extrapolated from data in table 1 and used in the calculation). Since fetal blood is relatively more acidic than maternal blood at delivery,[25] an ion-trapping effect will tend to produce a maternal–fetal drug equilibrium in favor of the fetus. Therefore, also shown in table 4 are theoretical R values calculated assuming a *p*H difference (7.4–7.2) between maternal and fetal plasma and using a modified form of the Henderson-Hasselbalch equation [1] (*i.e.*, $C_{upf} > C_{mpf}$ at equilibrium). The latter calculation assumes, however, that binding does not vary over the *p*H range considered. We also emphasize that the values quoted in table 4 are approximate, since they largely depend upon extrapolation of available data. Bearing in mind this qualification, a reasonable similarity appears to exist between theoretical ratios and the experimental values noted for lidocaine. Experimental ratios for bupivacaine obtained with Group II subjects (see table 3) are also fairly consistent with the corresponding theoretical ratios, although results with Group I subjects are significantly higher (see table 2).

In general, the results of the preceding calculations would seem to lead to the conclusion that equilibrium distribution of the local anesthetics between maternal and fetal plasma is essentially achieved. Furthermore, the well-documented observation that appreciable umbilical levels of the drugs are quickly established and that, thereafter, umbilical/maternal ratios show relatively little change with time (see references 5, 6, 8, 9, 10, 13, 14, and tables 2 and 3), suggests that equilibration is rapid. This conclusion appears to apply irrespective of the extent of plasma binding of the different agents, implying, therefore, that although plasma binding may influence equilibrium distribution of the drugs between maternal and fetal plasma, owing to differential fetal–maternal binding capacities, it has less influence on the rate of approach to equilibrium. Perhaps any retarding effect of the extensive binding of bupivacaine on the speed of transplacental equilibration is offset by the relatively high lipid solubility of the drug.

Any discrepancy between calculated and experimental R values must be related to the assumptions upon which the calculations are based. However, we submit that the relative plasma-binding properties of the local anesthetics considered herein account, in part, for their transplacental distribution. Undoubtedly, the complexities of the fetoplacental circulation also contribute to observed variations in the umbilical/maternal concentration ratios of these drugs.[6]

## Drugs

**THIOPENTAL** Elderly patients (average age 65 years) slept considerably longer than younger patients (average age 32 years) following a standardized dose of thiopental (4.5 mg/kg). The elderly patients also had lower plasma concentrations of thiopental at the moment of awakening. No relationship between duration of sleep and body weight could be demonstrated. (*Oduah, M.: Potency and Duration of Action of Thiopental in Man in Relation to Age, Der Anaesthesist 18: 308 (Sept.) 1969.*)