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Effects of Changes in Maternal–Fetal pH *on the Transplacental Equilibrium of Bupivacaine*

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Increases in the maternal–fetal *p*H gradient that may occur during labor and delivery may increase the fetal concentration of local anesthetics. The authors evaluated effects of *p*H changes on the transplacental concentration equilibrium of bupivacaine. They increased the maternal–fetal *p*H gradient in each of six pregnant ewes from a control value of 0.15 to 0.54 by hyperventilating the lungs of the ewe and infusing lactic acid into her fetus. After infusion of bupivacaine, 0.15 mg/kg, intravenously into the mother, the drug rapidly appeared in fetal blood, with values significantly increased over control values at 1 and 5 min. The fetal/maternal (f/m) ratios were increased significantly at 5, 15, and 30 min. The f/m ratios had stabilized by 15 min in both control and experimental states, suggesting that equilibrium had been achieved. The consistently low f/m ratios are explained by the presumed similarity of the ovine maternal and fetal protein binding rates to those of man. It is concluded that the maternal and fetal *p*H values are major factors in the determination of the f/m ratios. (Key words: Acid–base equilibrium: fetal acidosis; maternal alkalosis. Anesthesia, obstetric. Anesthetic techniques, regional: epidural. Anesthetics, local: bupivacaine. Placenta.)

BUPIVACAINE is commonly used in obstetrics because it has been shown to be devoid of neonatal effects following maternal lumbar epidural anesthesia.[1,2] This lack of effect appeared to be associated with a lower fetal drug concentration when compared with lidocaine and mepivacaine. Fetal drug concentrations are affected by blood *p*H. Brown *et al.*[3] associated fetal acidosis with high blood concentrations of local anesthetic. Biehl *et al.*[4] confirmed experimentally that fetal acidosis increases fetal lidocaine concentration and the fetal/maternal (f/m) concentration ratio following maternal administration. A previous report from our laboratory which, in addition, included maternal alkalosis in order to increase the maternal–fetal *p*H gradient, showed similar results.§

Well recognized is the consistently low f/m ratio of bupivacaine as compared with other local anesthetics.[5–7] The ratios are characteristic for individual local anesthetics although variations occur with the site and mode of administration. These ratios suggest that a concentration equilibrium is established between the maternal and fetal circulations.[7] In addition to *p*H, maternal and fetal protein binding are related to the low concentration of bupivacaine that results in fetal blood.[7–9] However, the maternal and fetal *p*H changes that may occur during labor and delivery may increase the fetal blood concentration of bupivacaine to an undesirable level. Consequently, we have produced a large maternal–fetal *p*H gradient to determine the increase in the fetal bupivacaine concentration and the f/m ratio that results following a single intravenous infusion of bupivacaine in the pregnant ewe. A stable f/m ratio would suggest achievement of a maternal and fetal concentration equilibrium.[7]

Methods

Using general anesthesia, we prepared six pregnant ewes whose gestation of 120 days was predetermined by use of the induced-ovulation technique.[10] After fasting for 24 hours, the ewes were anesthetized with thiopental, 500 mg, and succinylcholine, 20 mg. Following endotracheal intubation, respiration was controlled using a Bird Mark VII Respirator® driving a Ventimeter® (Air Shields). The apparatus was connected to a circle carbon dioxide absorption system and anesthesia maintained with halothane, 1 per cent, in nitrous oxide and oxygen, 4:2 l/min. Using aseptic technique, we performed a hysterotomy through a small midline incision. A fetal hind limb was exposed and polyethylene catheters, OD 0.050 in, were inserted into both a femoral artery and a vein. The uterus and abdomen were closed around the catheters. In addition, a branch of a maternal femoral artery was exposed and cannulated. All catheters were tunnelled subcutaneously and exteriorized through the left flank. Patency of the catheters was maintained by daily flushing with heparin, 10 IU/ml, in saline solution. The animals were allowed to recover for 48 hours.

After obtaining control measurements, we induced maternal respiratory alkalosis and fetal acidemia the following day. A tracheostomy was established during local anesthesia with lidocaine, 0.5 per cent, 5

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§ Radosevich FA, Kennedy RL, Turner T, et al: The effect of maternal and fetal *p*H changes on placental transfer of lidocaine (abstr). Annual Meeting of the American Society of Anesthesiologists, 1976, pp 533–534.

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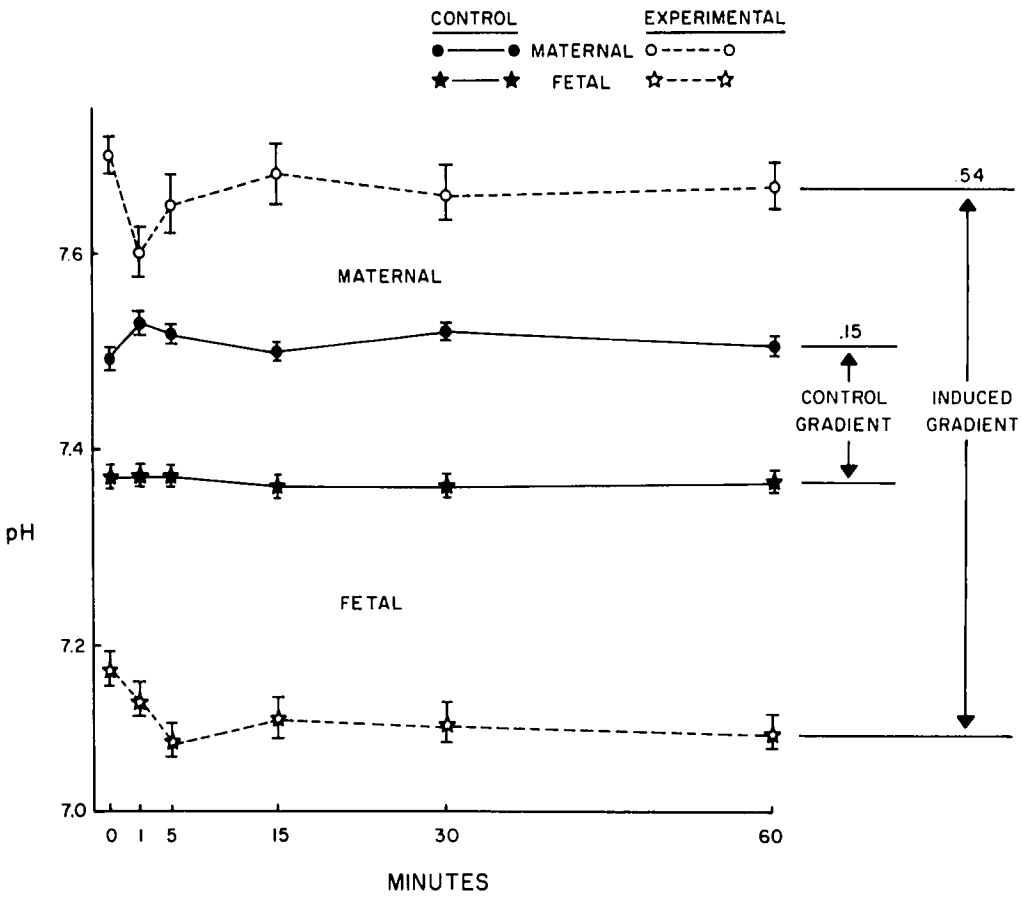

FIG. 1. *p*H and *p*H gradient during the control and altered *p*H states (mean ± SE).

ml. Through the tracheostomy we hyperventilated the ewe's lungs with the same apparatus used for anesthesia except that air, 15 l/min, was substituted for anesthetic gases. The maternal blood P_{CO_2} decreased from a control value of 29 ± 1 to 19 ± 1 torr, and P_{O_2} increased from 87 ± 1 to 101 ± 2 torr. To decrease the *p*H of fetal blood rapidly, we infused lactic acid, 0.25 M, in lactated Ringer's solution, into the fetus at a rate of 5–7 ml/min, depending on the responses of the fetal heart rate and blood pressure. The rate was decreased to 0.4–1 ml/min for maintenance. The fetal blood P_{CO_2} decreased from 45 ± 1 to 38 ± 2 torr and P_{O_2} changed from 17 ± 2 to 18 ± 1 torr. The increase in fetal base deficit from 1.1 ± 0.5 to 14.8 ± 0.6 mEq/l was appropriate for lactic acid infusion. The maternal–fetal *p*H gradient increased from a control of 0.15 to 0.54 as a result of the induced maternal alkalosis and fetal acidemia (fig. 1).

During both control and altered-*p*H states, we infused bupivacaine, 1.5 mg/kg, over a 1-min period into a maternal jugular vein. Maternal and fetal arterial pressure values were continuously monitored. Fetal heart rate was recorded with a cardiotachometer. Maternal and fetal arterial blood samples, 2 ml, were withdrawn simultaneously at 0, 5, 15, 30, and 60 min. After *p*H and blood-gas determinations on each sample, the remainder of the sample was analyzed for bupivacaine concentration by gas chromatography.[11]

The data were analyzed using three-factor analysis of variance. The Student *t* test was used for individual comparisons. $P < 0.05$ was considered significant.

Results

Following bupivacaine injection during both the control state and the state of combined maternal respiratory alkalosis and fetal acidemia, the drug appeared rapidly in fetal arterial blood and reached its maximum level at 1 min (fig. 2). The rapid decline in concentration, representing distribution to the central compartment,[12] appeared to end in the fetus at 15 min and was less pronounced in the mother at 30 min. The increased *p*H gradient increased the fetal concentration of bupivacaine significantly at 1 and 5 min. At 60 min the fetal blood concentrations during the control and experimental states were almost identical, at 0.06 and 0.07 μg/ml, even though the *p*H gradient was constant.

The f/m ratios were increased significantly at 5, 15,

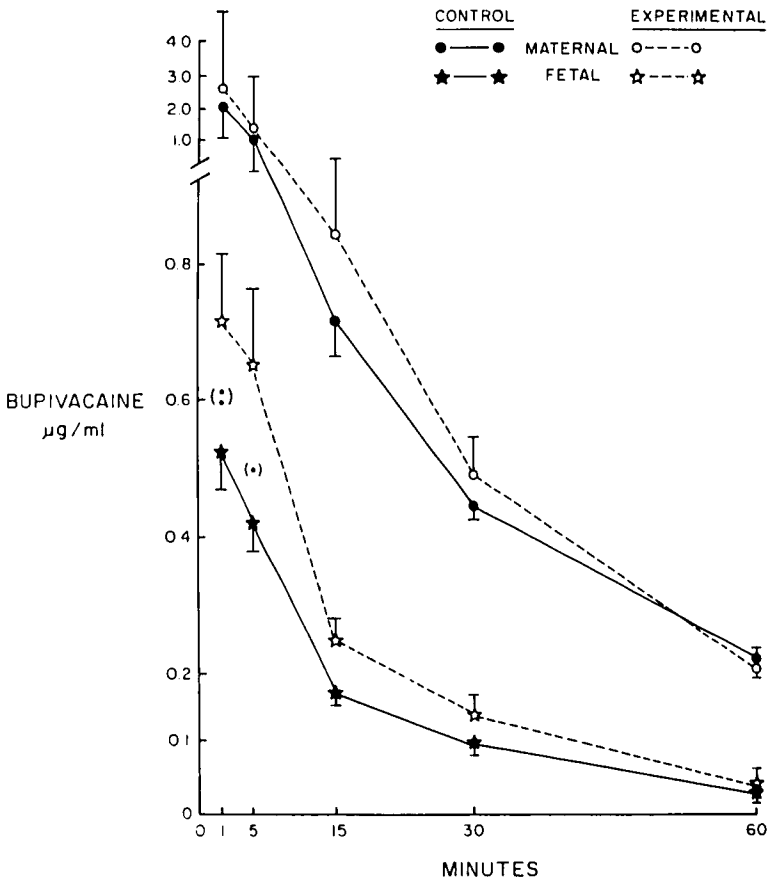

FIG. 2. Maternal and fetal bupivacaine decay curves during the control and experimental states (mean ± SE). $*P < 0.05$; $**P < 0.01$.

and 30 min (fig. 3). The higher f/m ratio at 5 min occurred during the phase of drug distribution to the central compartment. At 15 min, corresponding to the beginning of the slow-elimination phase, the f/m ratios stabilized at 0.23–0.26 during the control period and 0.30–0.34 during the experimental period. The increased ratios were significant at 5, 15, and 30 min.

Variations in maternal blood pressure and heart rate occurred, but were not significant. In the acidemic fetus, fetal tachycardia (201 ± 14 beats/min) developed, and varied between 176 and 187 beats/min following bupivacaine injection. This tachycardia was associated with a higher mean blood pressure, ranging from 56 to 63 torr more than the control values of 50 to 56 torr. Both fetal heart rate and fetal blood pressure changes were significant at 0, 15, and 30 min.

Discussion

This study evaluated only the transplacental relationship of maternal and fetal bupivacaine concentrations as it was affected by *p*H changes. Consequently, total fetal accumulation of the drug cannot be inferred from our results. In addition, the acidemia in this study was exogenous and would differ from fetal acidosis occurring during fetal distress. In acidosis, the tissue compartment, since it is the origin of lactic acid, can be presumed to be more acidic. Hence, another *p*H gradient would occur between the intracellular and extracellular compartments, which then could favor higher tissue concentrations.

Biehl *et al.*[4] employed a constant infusion of lidocaine when studying the effect of fetal acidosis on fetal blood concentrations. A single injection, rather than constant infusion, permitted us to observe the rapid appearance of bupivacaine in fetal blood. In addition, we observed the f/m ratios during the distribution phase as well as the elimination phase of drug distribution.[12]

The concept of a maternal–fetal equilibrium is controversial. Ralston and Shnider,[6] in their comprehensive review, presented evidence that equilibrium does not occur. Impedance to placental transfer by ionization, protein binding, and redistribution to fetal tissue were offered as explanations for the maternal–fetal tissue concentration gradient. Tucker *et al.*,[7] on the other hand, concluded that a fetal-to-maternal plasma concentration equilibrium was quickly established for each local anesthetic, and the f/m ratios showed little change with time. They demonstrated a close relationship between reported f/m ratios and

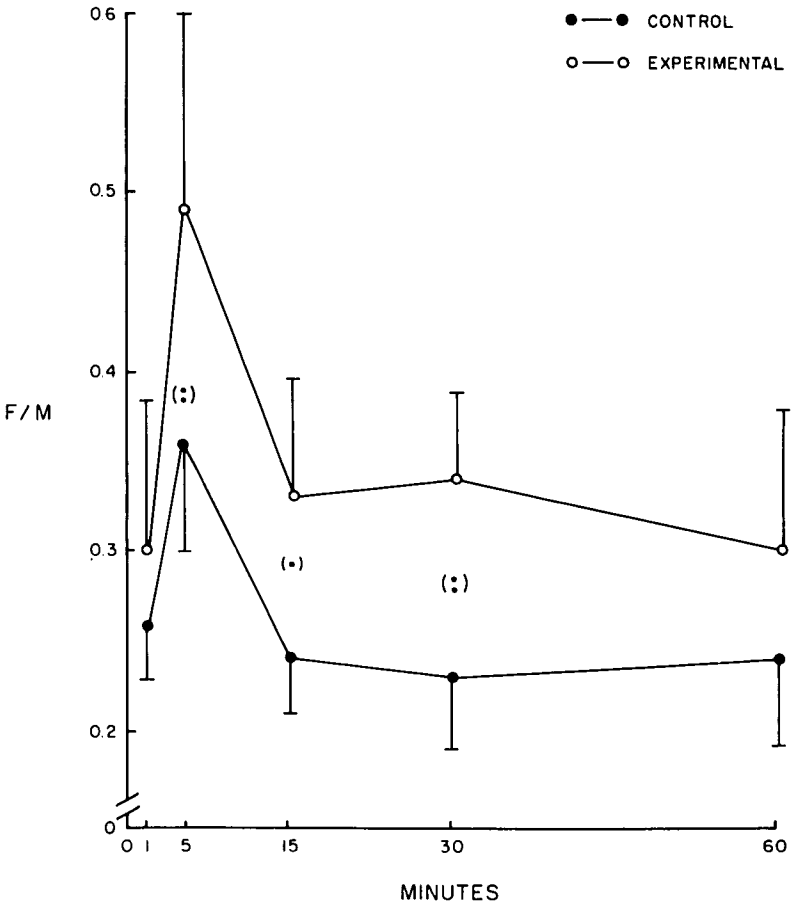

FIG. 3. Fetal/maternal (f/m) ratios of bupivacaine concentrations during the control and experimental states. (mean ± SE). *$P < 0.05$; **$P < 0.01$.

those calculated from their data for protein binding in maternal and fetal blood.

Calculation of the f/m ratio using our data supports Tucker's concept if it is assumed that equilibrium occurs. Concentrations of unionized free drug in maternal and fetal blood become nearly equal. Upon reaching fetal blood, the drug enters into another equilibrium reaction with the available hydrogen ion and becomes protein-bound, depending on the binding rate of the fetal plasma protein and erythrocytes. Total concentration is measured, and not individual components of free, ionized, and bound drug. The total concentration in maternal (C_m) and fetal (C_f) blood can be determined for the pH-dependent contribution to the f/m ratio by solving the Henderson-Hasselbalch equation with known pH values for both the maternal ($p\mathrm{H_m}$) and fetal ($p\mathrm{H_f}$) blood. The following formula results[3,13]:

$$\frac{f}{m} = \frac{C_f}{C_m} = \frac{1 + 10^{pK-p\mathrm{H_f}}}{1 + 10^{pK-p\mathrm{H_m}}}$$

The added effect of protein binding leaves a free fraction (FF), which then equilibrates across the placenta. The product of the total maternal concentration and the maternal free fraction (FF_m) will then equal that of the fetal concentration and the fetal free fraction (FF_f).

$$C_m \times FF_m = C_f \times FF_f$$

By rearrangement, the formula for the f/m ratio for protein binding becomes:

$$\frac{f}{m} = \frac{C_f}{C_m} = \frac{FF_m}{FF_f}$$

The formulas may be combined:

$$\frac{f}{m} = \frac{C_f}{C_m} = \frac{1 + 10^{pK-p\mathrm{H_f}}}{1 + 10^{pK-p\mathrm{H_m}}} \times \frac{FF_m}{FF_f}$$

The free fraction is obtained by subtracting the percentage bound from 100 and dividing by 100. Assuming that sheep plasma binds bupivacaine to the same extent as human plasma, 95 per cent by adult and 66 per cent by fetal blood,[7] FF_f becomes 0.34 and FF_m becomes 0.05. Substituting our observed pH values (control: $p\mathrm{H_m}$ 7.52, $p\mathrm{H_f}$ 7.37; induced: $p\mathrm{H_m}$ 7.66, $p\mathrm{H_f}$ 7.12), the calculated f/m ratios show an increase from 0.20 to 0.41, which is in the range of our observed results.

The protein-binding factor in this example is 0.05/0.34, or 1/7. A high degree of binding by maternal

plasma thereby provides a small free fraction as the numerator and a lesser degree of binding by the fetal plasma produces a larger denominator. This differential maternal and fetal binding capacity is therefore necessary for the observed attenuation of the fetal blood concentration. Mather *et al.*[8] found that maternal protein bound approximately twice as much bupivacaine per gram as fetal protein. Thomas *et al.*[9] demonstrated that variations in the f/m ratios were related to the quantitative variations in plasma protein from subject to subject.

Protein binding is not constant, however, and decreases with higher drug concentrations. Maximum binding occurs at less than 3 μg/ml,[14] so that concentration does not account for the discrepancy between the calculated and observed f/m ratios. Protein binding varies with *p*H,[15] so that increased binding in maternal blood during alkalosis and decreased binding in fetal blood during acidosis could be presumed. These variations may explain why a twofold increase did not occur as calculated. Protein binding, in addition to *p*H changes, appears to be a major factor determining the f/m ratios. However, the extent of protein binding of local anesthetics by sheep plasma has not yet been determined.

That there was little impediment to placental passage was suggested by the appearance of maximum fetal concentrations at 1 min despite the two widely different *p*H gradients and *p*H-dependent unionized fractions. In addition, during the period of distribution to the highly perfused organs,[12] the f/m ratios were higher in both states (fig. 3). This increase indicates that the fetus received a higher proportion of the drug early in the distribution process. At 15 min, which appeared to be the beginning of the elimination phase, the f/m ratios were found to be stable, suggesting that equilibrium had been achieved. This stability occurred while maternal and fetal levels continued to decline.

Blood flow can be assumed to have been altered, as shown by the changes in blood pressure and heart rate. Levinson *et al.*[16] demonstrated that maternal hyperventilation, produced in a manner similar to the hyperventilation in our protocol, decreased uterine blood flow 25 per cent as a result of the mechanical effect of ventilation. Because the f/m ratios during the control and experimental states were parallel, we assume that uterine and umbilical blood flow variations were not sufficient to limit placental passage.

Understanding of the mechanisms controlling fetal blood concentrations and f/m ratios is only one step in the development of the knowledge of placental transfer of drugs. Conclusions regarding the rate of passage must await definitive studies. The evidence we present suggests that the establishment of a transplacental equilibrium is rapid and that the fetal concentration as a fraction of the maternal concentration is regulated by physicochemical factors. The effect of drug ionization is described, but the role of protein binding using the ovine model requires knowledge of maternal and fetal protein binding rates in this species. Because of the low f/m ratio, we anticipate that the binding rates for bupivacaine will be found to be similar to those of human plasma protein.

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