MATERNAL AND NEONATAL EFFECTS OF 1% AND 2% MEPIVACAINE
FOR LUMBAR EXTRADURAL ANALGESIA

R. B. CLARK, G. L. JONES, D. L. BARCLAY, F. E. GREIFENSTEIN AND P. E. MCAINCH

SUMMARY
Continuous lumbar extradural analgesia with mepivacaine was administered to two groups of patients in normal labour. One group (26 patients: 1% mepivacaine) received a mean total dose of 342 mg (4.93 mg/kg) per patient, and developed a mean blood concentration of mepivacaine at delivery of 1.82 \( \mu \text{g/ml} \). The neonatal umbilical vein concentration was 0.84 \( \mu \text{g/ml} \). The other group (30 patients: 2% mepivacaine) received a mean total dose of 776 mg (11.65 mg/kg) per patient, and developed a mean blood concentration of mepivacaine at delivery of 3.47 \( \mu \text{g/ml} \). The neonatal umbilical vein concentration was 2.61 \( \mu \text{g/ml} \). Four of the infants of mothers who received 1% mepivacaine were depressed (1-min Apgar score 6 or less), and six of the other group were depressed also. Usually, depression appeared to be related to obstetric factors, rather than to analgesia. Eleven of the 56 infants had umbilical vein mepivacaine concentrations of 3 \( \mu \text{g/ml} \) or greater; of these, three were depressed. This does not agree with the concept that the toxic threshold for mepivacaine is 3 \( \mu \text{g/ml} \). In both groups a significant linear correlation was obtained between umbilical vein concentration and total dose of mepivacaine. A maximal dose of 12 mg/kg maternal weight in the non-obese or 12 mg/kg lean body mass in the obese is suggested for continuous extradural analgesia with mepivacaine, although healthy mothers and infants may tolerate much more.

One of the few disadvantages of lumbar extradural analgesia in obstetrics is the absorption and distribution of local anaesthetic agents, resulting in detectable blood concentrations in both mother and foetus (Hehre, 1969; Lurie and Weiss, 1970; Poppers, 1975). In small amounts these drugs have little systemic effect, but higher blood concentrations are said to be associated with toxicity, especially in the neonate (Morishima et al., 1966; Shnider and Way, 1968). We decided to measure maternal and neonatal mepivacaine blood concentrations using 1% and 2% mepivacaine, and to note any systemic effects associated with these concentrations.

METHODS
Normal obstetric patients in labour at term were studied. The foetus was in the vertex presentation in all cases. An intravenous infusion of dextrose 5% in water was begun, and heart rate, arterial pressure and respiratory frequency were recorded. After permission was obtained from the patient, lumbar extradural analgesia was administered, with the patient in the sitting position, using 1% mepivacaine (26 cases) or 2% mepivacaine (30 cases). The extradural space was identified by the loss of resistance technique (Moore, 1964), and a test dose of mepivacaine 2 ml was administered. When this did not produce detectable analgesia, a further dose (usually 14 ml) was injected through a Tuohy needle. A plastic catheter was threaded about 2.5 cm through the needle, the needle was removed and the catheter was taped in place. Further injections (10–12 ml) were made through the catheter. Using this technique, the initial level of anaesthesia extended usually to the 10th thoracic dermatome.

To facilitate bilateral spread of the mepivacaine, the patients were supine during labour. The progress of labour was assessed by pelvic examinations and the maternal and foetal heart rate were recorded every 5–15 min. Foetal heart sounds were auscultated frequently. In both groups of patients, additional doses of mepivacaine were given every hour. Maternal arterial hypotension, if it occurred, was treated by left uterine displacement and infusion of lactated...
Ringer's solution and, if this was unsuccessful, by the i.v. injection of ephedrine.

The analysis of the mepivacaine concentration in blood was similar to that described by several authors (Maes, Kananen and Sunshine, 1969; Asling et al., 1969; Tucker, 1970). The basic steps were: addition of an internal standard (lignocaine) to the blood, alkalinization with sodium hydroxide, and extraction with ether. This yielded an ether solution of the standard, the drug being studied, and whatever blood components were soluble in ether. This ether phase was separated from the blood and extracted with dilute hydrochloride acid. Thus, quantitative conversion of the drugs to the ether-insoluble hydrochlorides and their solution in the aqueous phase was effected. The undesired blood constituents remained in the ether phase, which was separated and discarded. The aqueous phase was then alkalinized and extracted with a fresh aliquot of ether. The ether phase was removed and evaporated to dryness in a conical tube, and the residue was taken up in a few ml of carbon disulphide and injected into the gas chromatograph (Barber-Coleman Series 5000 with a hydrogen flame detector). The ratio of drug to standard peak areas was calculated and compared with a calibration line which had been prepared using in vitro experiments with known quantities of the drugs.

RESULTS

Nineteen of the 26 patients in the 1% group and 22 patients of the 30 in the 2% group were primigravidae. Values for the weight, age, mepivacaine dose and concentration of the patient and the infant, and the Apgar score are given in table I. Umbilical artery and vein acid-base values at birth are given in table II. These values are similar to previously reported findings using general anaesthesia for delivery (Clark et al., 1970). Both the 1% and 2% mepivacaine groups are similar as regards maternal age, weight, duration of extradural analgesia and duration of labour. The mean total dose of mepivacaine in the 2% group was 2.3 times that of the 1% group (776 mg v. 342 mg, P < 0.001 with the Student t test), and the maternal dose of mepivacaine (mg/kg) was 2.3 times higher also (11.6 mg/kg v. 4.9 mg/kg, P < 0.001). The maternal venous concentration of mepivacaine was significantly higher in the 2% group than the 1% group (3.47 µg/ml v. 1.82 µg/ml, P < 0.02). This was true also for the umbilical vein values (2.61 µg/ml v. 0.84 µg/ml, P < 0.001). There were six depressed infants in the 2% group (1-min score 6 or less) and four in the 1% group.

Blood was obtained for mepivacaine analysis from the umbilical artery of seven of the 2% mepivacaine infants. The concentration averaged 84% of the umbilical vein value.

<table>
<thead>
<tr>
<th>Table I. Maternal and neonatal data (mean values (±1 SD))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mepivacaine concentration</td>
</tr>
<tr>
<td>Number of patients</td>
</tr>
<tr>
<td>Age (yr)</td>
</tr>
<tr>
<td>Weight (kg)</td>
</tr>
<tr>
<td>Total dose mepivacaine (mg)</td>
</tr>
<tr>
<td>Dose of mepivacaine (mg/kg maternal weight)</td>
</tr>
<tr>
<td>Dose of mepivacaine (mg/hr)</td>
</tr>
<tr>
<td>Dose of mepivacaine (mg/kg/hr)</td>
</tr>
<tr>
<td>Interval first dose mepivacaine to delivery (min)</td>
</tr>
<tr>
<td>Interval last dose mepivacaine to delivery (min)</td>
</tr>
<tr>
<td>Duration first stage of labour (hr)</td>
</tr>
<tr>
<td>Duration second stage of labour (min)</td>
</tr>
<tr>
<td>Maternal venous mepivacaine concentration at delivery (µg/ml)</td>
</tr>
<tr>
<td>Umbilical venous mepivacaine concentration at delivery (µg/ml)</td>
</tr>
<tr>
<td>1-min Apgar scores 6 or less</td>
</tr>
<tr>
<td>Base excess (m-equiv/litre)</td>
</tr>
<tr>
<td>pH (units)</td>
</tr>
<tr>
<td>Po2 (mm Hg)</td>
</tr>
<tr>
<td>Pco2 (mm Hg)</td>
</tr>
<tr>
<td>Base excess (m-equiv/litre)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table II. Umbilical artery and vein acid-base values at birth (mean values ±1 SD). Blood aspirated from doubly clamped sections of umbilical cord</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mepivacaine concentration</td>
</tr>
<tr>
<td>pH (units)</td>
</tr>
<tr>
<td>Po2 (mm Hg)</td>
</tr>
<tr>
<td>Pco2 (mm Hg)</td>
</tr>
<tr>
<td>Base excess (m-equiv/litre)</td>
</tr>
</tbody>
</table>

were six depressed infants in the 2% group (1-min score 6 or less) and four in the 1% group.
Mepivacaine 1%

Maternal response. Four of the mothers exhibited shivering, but none showed any further signs of central nervous system stimulation. Arterial hypotension (systolic pressure less than 100 mm Hg) occurred in three patients, and was treated by left uterine displacement and fluid infusion. In addition, ephedrine was given to one of these patients. The initial analgesic levels were: fourth thoracic dermatome (three patients); T6, five; T8, three; T10, 10 patients; and T12, five. In one patient labour was augmented by oxytocin infusion.

Neonatal response. Four of the 26 infants had 1-min Apgar scores of 6 or less (table I). All had 5-min scores greater than 6. There were five spontaneous deliveries, 15 deliveries by elective low forceps, and six deliveries following rotation of the head with Keilland's forceps. One infant was delivered with a tight nuchal cord, which required clamping and cutting before delivery, and six were delivered with loose nuchal cords. Of the depressed infants, one was delivered with a tight nuchal cord, one following a difficult rotation of the head, one had spina bifida, and one was the child of the mother who received ephedrine.

Mepivacaine accumulation. The maternal dose of mepivacaine (mg/kg body weight) was plotted against umbilical vein mepivacaine concentrations (fig. 1). As more mepivacaine was administered to the mother, the umbilical vein mepivacaine concentration increased \( r = 0.55 \). The total dose of mepivacaine for each mother was plotted against umbilical vein blood mepivacaine concentration \( r = 0.44; P < 0.05; u = 0.157 + 0.002 \) total dose).

The relationship between umbilical vein mepivacaine concentration, and 1-min Apgar score is shown in figure 2. Only one infant had an umbilical vein concentration greater than 3 \( \mu g/mL \). All four of the depressed infants had low mepivacaine concentrations.

Mepivacaine 2%

Maternal response. Six patients exhibited fairly pronounced shivering, but none showed any further signs of central nervous system stimulation. Fourteen of the 30 patients became hypotensive after the block was established (systolic arterial pressure decreased below 100 mm Hg). Treatment was prompt and resulted in a rapid return to the previous arterial pressure. Twelve patients responded to left uterine displacement and fluid infusion; two required i.v. injection of ephedrine in addition to the above measures. Two of the six infants whose mothers became hypotensive had 1-min Apgar scores of 6 or less. The initial analgesic levels were: fourth thoracic dermatome (two patients); T6, four; T8, 10 patients; T10, 11 patients; and T12, three. In three patients labour was augmented by oxytocin.

Neonatal response. Six of the 30 infants had a 1-min Apgar-score of 6 or less (table I). Three of the 30 infants had a 5-min Apgar score of 6 or less (all had a 1-min score of 6 or less). There were four spontaneous deliveries, 21 deliveries by elective low forceps, and five deliveries after rotation of the head with Keilland's forceps. Three infants were delivered...
with a tight nuchal cord, which required clamping and cutting before delivery. Two of the six depressed infants had a tight nuchal cord, two required Kielland rotation, and one was listed as a difficult delivery. The sixth depressed infant had an umbilical vein mepivacaine concentration at delivery of 3.36 μg/ml, and an umbilical artery pH of 7.03 units.

Mepivacaine accumulation. The maternal dose of mepivacaine (mg/kg body weight) was plotted against the umbilical vein mepivacaine concentration (fig. 3).

![Fig. 3. Mepivacaine 2%—Relationship between the total dose of mepivacaine administered to mother and umbilical vein mepivacaine concentration at delivery. The 30 study patients are indicated by closed circles. In order to obtain data for lower doses, several other patients were investigated using a single injection of mepivacaine 2% for delivery. These are indicated by open circles. Thus, 34 points appear on this figure. Correlation coefficient \( r = 0.79, uv = 0.1899 + 0.2046 \text{ dose/kg}, \) \( P < 0.05. \) The slope of the regression line is 0.2046.]

There was a positive correlation \( (r = 0.79). \) The total dose of mepivacaine in each mother was plotted against umbilical vein blood mepivacaine concentration \( (r = 0.82; P < 0.05; uv = 0.004 + 0.003 \text{ total dose}). \)

The relation between umbilical vein concentration and 1-min Apgar scores is shown in figure 4. Of the six depressed infants, three had umbilical vein mepivacaine concentrations less than 3 μg/ml. Of the 11 infants with umbilical vein concentrations of 3 μg/ml or above, only three were depressed.

**DISCUSSION**

We have shown that higher maternal and neonatal blood concentrations of mepivacaine occurred when 2% mepivacaine was used for extradural analgesia, compared with the use of 1% mepivacaine. The drug accumulates in a predictable fashion, indicating a very slow breakdown. Tucker and colleagues (1972) reported adult blood concentrations almost as high at 120 min after extradural block as at 20 min. Moore and colleagues (1968) observed a stepwise accumulation with mepivacaine when caudal analgesia was used. The duration of analgesia was about the same in both our groups (142 min v. 187 min, table 1), but the 2% group had much higher blood concentrations, as a result of the higher concentration.

Despite higher blood concentrations in the 2% group, the rate of depression was about the same (six infants in the 2% group, four in the 1% group) and virtually all instances of depression could be explained by obstetric factors. Acid–base data were virtually the same in both groups. Although many of the infants in both groups had high blood mepivacaine concentrations, they were not depressed. Thus, on the basis of the Apgar score, we did not reach a toxic threshold for the infants.

Morishma and colleagues (1966), using 1.5% mepivacaine for extradural analgesia, noted that 12 infants were depressed out of 56; five of these 12 had umbilical vein mepivacaine concentrations greater than 3 μg/ml. The toxic
threshold for both mepivacaine and lignocaine seems to have been established at 3 \( \mu g/ml \) (Hyman and Shnider, 1971).

Twelve of the 56 infants in this study had umbilical vein mepivacaine concentrations of 3 \( \mu g/ml \) or greater at birth, and of these only three were depressed. The toxic threshold for the neonate (as indicated by Apgar scoring) appears to be more than 3 \( \mu g/ml \) in umbilical vein blood and is probably between 3 and 8 \( \mu g/ml \). Finster and colleagues (1965) found that in four infants accidentally intoxicated with mepivacaine during attempted caudal analgesia, clinical signs of toxicity disappeared and the e.e.g. became normal when neonatal blood concentrations decreased to 8 \( \mu g/ml \). Thus, an umbilical vein blood concentration of 3 \( \mu g/ml \) mepivacaine is not prima facie evidence of mepivacaine depression. The toxic effects of lignocaine occur in conscious subjects at a plasma concentration in excess of 5 \( \mu g/ml \) (Scott et al., 1972).

Out of 56 infants in our study, mepivacaine blood concentrations of 3 \( \mu g/ml \) or greater were found in 12, while 44 had concentrations less than 3 \( \mu g/ml \). Twenty-five per cent of those infants (3 out of 12) whose mepivacaine concentration was 3 \( \mu g \) or above were depressed, as against 16\% (7 out of 44) of those with less than 3 \( \mu g/ml \). Thus, the depression rate was virtually the same above and below 3 \( \mu g/ml \), indicating that 3 \( \mu g/ml \) is not the toxic threshold. If it were, the majority of infants whose concentration was above 3 \( \mu g/ml \) would have been depressed.

Despite this evidence that normal infants can tolerate higher quantities of mepivacaine than was thought previously, limits should be imposed on the amount of mepivacaine used during continuous extradural analgesia. In a previous study Romine, Clark and Brown (1970) recommended that a total dose of 600 mg be not exceeded. Moore and colleagues (1968) recommend a limit of 1500 mg. Assuming that the weight of the patient is 60 kg, a total dose of 600 mg would be equivalent to 10 mg/kg body weight. From figures 1 and 3 we would expect that dose to produce an umbilical vein concentration of approximately 2 \( \mu g/ml \). If a concentration of 3 \( \mu g/ml \) in the umbilical vein were the maximum (and we have shown that this can often be exceeded without obvious depression), then the patient should not receive more than 12 mg/kg. However, drug depression is not an all or nothing phenomenon. Infants in good condition can tolerate larger amounts of a drug than can compromised infants. Some of the infants in our study were well in spite of the mother receiving more than mepivacaine 1000 mg (14-16 mg/kg). It would seem prudent, however, not to exceed 10-12 mg/kg. This is easier with the segmental approach (Bonica, 1967) rather than the standard continuous block, which we used in this study.

When the dose (mg/kg/hr) of mepivacaine was determined (table 1) and plotted against umbilical vein mepivacaine concentration, a significant correlation (0.61) was obtained. However, one would not predict high blood concentrations of mepivacaine with usual clinical doses, unless several injections were made over a period of several hours, so the concept of dose in mg/kg seems much the more useful index.

The total dose of mepivacaine was plotted against umbilical vein blood concentration also. The correlation coefficient for the 1% group was 0.44, and that of the 2% group, 0.82. Thus it made little difference whether total dose or dose in mg/kg was used, although it is common practice to calculate other drug dosage on a body weight basis. Scott and others (1972) have shown that body weight is an important determinant of the blood concentration of local anaesthetics only if lean body mass is considered. An increase in weight because of obesity does not change the concentration (our patients were fairly homogeneous as regards weight). Obviously, if large differences in lean body mass exist (as in comparing children and adults, or males and females) weight would be an important consideration. Therefore, in non-obese patients it would not matter whether the absolute dose were expressed in mg/kg or total dose. In the obese patient, expressing the maximum allowable dose as a function of total weight could result in an overdose. Therefore, a total of 12 mg/kg body weight in the non-obese or 12 mg/kg lean body mass in the obese is recommended by us.

The mean values of acid-base data in the two groups did not differ significantly from each other. This indicates that, despite the greater incidence of maternal hypotension, higher dermatome levels and higher mepivacaine concentrations in the 2% group infants, they were not affected adversely. The prompt restoration of maternal arterial pressure was probably responsible for this. The supine position was employed to ensure complete analgesia, despite our awareness that there is a high incidence of vena caval compression in this position. However no harm resulted from this action.

Higher foetal-maternal mepivacaine ratios were seen in the 2% group (0.75) compared with the 1% group (0.46). This is probably a result of the higher concentrations in the 2% group.
In our previous paper (Romine, Clark and Brown, 1970) we suggested a limit of 600 mg of mepivacaine for the mother. This conclusion was based on the Apgar scores which were reduced in cases in which the 600 mg total was exceeded. On the other hand, the patients who received more than 600 mg had longer labours. In this present study, the duration of labour was almost the same for both groups, and we have demonstrated that 600 mg can be exceeded. We recommend not exceeding 12 mg/kg in the lean patient and 12 mg/kg lean body mass in obese patients.

Our purpose is not to advocate large amounts of local anaesthetics for regional analgesia in the parturient. By carefully selecting only normal patients and controlling conditions, we have shown that high blood concentrations are not necessarily associated with clinically apparent neonatal effects.

ACKNOWLEDGEMENTS

Assistance was provided for this research by Mrs Carolyn Thompson, of the University of Arkansas Medical Center Division of Biometry. Mrs Celeste O'Neal typed the manuscript.

REFERENCES


BRITISH JOURNAL OF ANAESTHESIA

In our previous paper (Romine, Clark and Brown, 1970) we suggested a limit of 600 mg of mepivacaine for the mother. This conclusion was based on the Apgar scores which were reduced in cases in which the 600 mg total was exceeded. On the other hand, the patients who received more than 600 mg had longer labours. In this present study, the duration of labour was almost the same for both groups, and we have demonstrated that 600 mg can be exceeded. We recommend not exceeding 12 mg/kg in the lean patient and 12 mg/kg lean body mass in obese patients.

Our purpose is not to advocate large amounts of local anaesthetics for regional analgesia in the parturient. By carefully selecting only normal patients and controlling conditions, we have shown that high blood concentrations are not necessarily associated with clinically apparent neonatal effects.

ACKNOWLEDGEMENTS

Assistance was provided for this research by Mrs Carolyn Thompson, of the University of Arkansas Medical Center Division of Biometry. Mrs Celeste O'Neal typed the manuscript.

REFERENCES


MEPIVACAINE IN OBSTETRIC ANALGESIA

MÜTTERLICHE UND NEONATALE WIRKUNGEN VON 1% UND 2% MEPIVAKAIN ALS EXTRADURALE LUMBAR-ANALGESIE

ZUSAMMENFASSUNG

EFECTOS MATERNALES Y NEONATALES DE MEPIVACAINA AL 1% Y 2% EN LA ANALGESIA EXTRADURAL LUMBAR

SUMARIO
Se administró analgesia extradural lumbar continua con mepivacaina a dos grupos de pacientes en el parto normal. Un grupo (26 pacientes) recibió mepivacaina al 1%, una dosis media total de 342 mg (4,93 mg/kg) por paciente, y desarrolló una concentración sanguínea media al alumbramiento de 1,82 μg/ml. La concentración venosa umbilical neonatal fue de 0,84 μg/ml. El otro grupo (30 pacientes) recibió mepivacaina al 2%, una dosis total media de 776 mg (11,65 mg/kg) por paciente, y desarrolló una concentración sanguínea media de mepivacaina en el alumbramiento de 3,47 μg/ml. La concentración venosa umbilical neonatal fue de 2,61 μg/ml. Cuatro de los niños de madres que recibieron mepivacaina al 1% estaban deprimidos (1 min Apgar marcó 6 o menos) y seis del otro grupo estaban también deprimidos. La depresión, en general, pareció mas relacionada con factores obstétricos que con la analgesia. Once de los 56 niños tenían concentraciones de mepivacaina venosa umbilical de 3 μg/ml o más; de ellos tres estaban deprimidos. Esto no coincide con el concepto previo de que el umbral tóxico para la mepivacaina es de 3 μg/ml. En ambos grupos se obtuvo una significativa correlación lineal entre la concentración venosa umbilical y la dosis total de mepivacaina. Se sugiere una dosis máxima de 12 mg/kg de peso maternal en las no obesas y de 12 mg/kg de masa de cuerpo magro en las obesas para analgesia extradural continua con mepivacaina, aunque las madres y los niños sanos pueden tolerar mucho más.