THE INCIDENCE OF DETECTABLE LEVELS OF MEPIVACAINE AND LIDOCAINE IN NORMAL OBSTETRIC PRACTICE

by

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A Thesis Submitted to the Faculty of the

COMMITTEE ON TOXICOLOGY

In Partial Fulfillment of the Requirements
For the Degree of

MASTER OF SCIENCE

In the Graduate College

THE UNIVERSITY OF ARIZONA

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ACKNOWLEDGMENTS

The author wishes to express her sincere appreciation and gratitude to Dr. Dean E. Carter whose guidance and valuable help made this work possible. Appreciation is also extended to Dr. Philip Walson for his help and guidance throughout the course of this study, and to Dr. Cornelius Steelink for his criticisms and suggestions.

The author also wishes to express her appreciation to Ms. Karen Bell, Dr. Charles Lox, and the staff of the Arizona Medical Center Medical Records Department, the Arizona Health Sciences Center Blood Bank and the Tucson Medical Center Blood Bank for their assistance in providing specimens and helping with the clinical data reviews.

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ABSTRACT

A gas chromatographic method was developed that quantitated microgram (μg) amounts of mepivacaine and lidocaine simultaneously in biological fluids.

The use of mepivacaine and lidocaine in normal obstetric practice was studied. To date, there have been no reports concerning the incidence of detectable levels of these agents in the cord blood of a large sampling of neonates in normal obstetric practice. Local anesthetics were detected in 117 of the 200 cord blood samples analyzed from two institutions. A review of the patients' charts at one hospital indicated that pudendal administration of lidocaine resulted in higher cord blood levels than a combination of pudendal and local anesthesia. No correlations were noted between the route of administration of mepivacaine and the resulting cord blood levels. The condition of the neonate as indicated by the Apgar Score was not related to the route of administration of either agent or to the blood levels at birth. The patients' charts from the other institution were not available for review.

INTRODUCTION

Regional block anesthesia is widely used to control pain during childbirth. The amide type local anesthetics are the most popular anesthetic agents. In the United States, Carbocaine (mepivacaine) and Xylocaine (lidocaine) are the most commonly used agents (Lancet 1974), while bupivacaine is used widely in Japan, South America and Europe (De Jong 1970, p. 104).

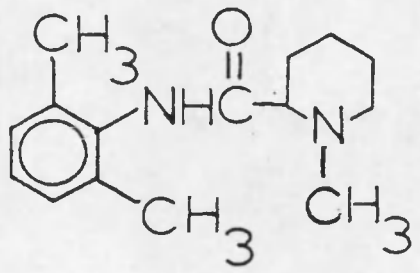
The use of regional block anesthesia has been regarded as offering major advantages to the mother and the fetus when compared to other approaches to obstetric analgesia. Even though certain advantages must be recognized, neurological sequelae and systemic toxic reactions have been reported. Bromage and Robson (1961) presented the first evidence of placental transfer of amide local anesthetics during obstetrical anesthesia. The numerous aspects of safety of these drugs have been examined by a number of investigators. This literature review will focus on the most commonly used local anesthetic agents (mepivacaine, lidocaine, bupivacaine), and the most widely used obstetrical block techniques. The pharmacokinetic properties of these drugs will be discussed in terms of maternal and fetal toxicity. The various regional blocks will be compared in terms of systemic absorption and potential toxicity.

Structure Activity Relationships

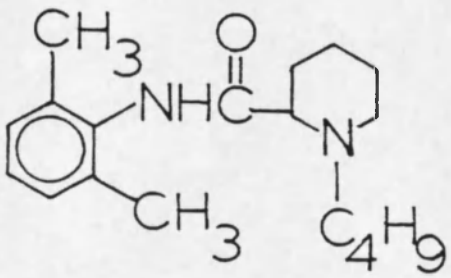
It has been determined that the most useful local anesthetics consist of: (a) an aromatic ring (lipophilic portion); (b) an intermediate chain; and (c) an amino group (hydrophilic portion). The local anesthetics are classified chemically by the type of linkage at the intermediate chain. The amide type anesthetics are distinguished from the esteratic type local anesthetics such as procaine, in that the amide type drugs are resistant to plasma enzymatic de-activation (Dipalma 1971, p. 194).

The pharmacologic properties of the various amide type local anesthetics are adjusted by modifications of the amide-linkage. Such modifications have resulted in the synthesis of mepivacaine, lidocaine, and bupivacaine (Fig. 1).

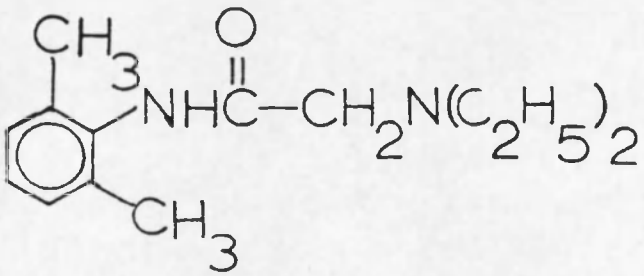
Reports in the literature indicate that bupivacaine is more potent than either mepivacaine or lidocaine. Most investigators estimated the relative activities of the drugs by comparing slopes obtained from regression analyses of plots of the dose versus the degree of anelgesia. Knox, North and Stephens (1961) reported that the potency of mepivacaine is 1.4 relative to lidocaine. The higher potency of mepivacaine as compared to lidocaine was confirmed by Henn (1960) following experiments in animals. After experiments using animals and humans, Henn and Brattsand (1966) reported that the potency of bupivacaine was 3.0 relative to mepivacaine.



Mepivacaine



Bupivacaine



Lidocaine

Figure 1. Structures of mepivacaine, bupivacaine and lidocaine.

In clinical studies, the three local anesthetics have been used to achieve local anesthesia by different routes of administration. It was shown that a lower dose of bupivacaine was required for analgesia in a number of studies. This lower dose resulted in lower blood concentrations of bupivacaine when compared to mepivacaine and lidocaine (Mazze and Dunbar 1966; Dhuner et al. (1965); Moore et al. 1970).

Bridenbaugh et al. (1974) reported that the duration of action of bupivacaine is longer than the duration of action of either mepivacaine or lidocaine. These findings were based on studies in animals. Clinical studies (Baskett and Carson 1974) have confirmed the results of Bridenbaugh et al. (1974). Intracutaneous experiments in humans indicated that mepivacaine had a longer duration of action (105 minutes) than lidocaine (68 minutes) (Henn 1960).

Absorption and Distribution

Local anesthetics affect all the neurons they contact. The ideal local anesthetic would block a painful impulse without production of irritation, nerve or tissue damage and with minimal systemic absorption from the site of action. When systemic absorption occurs, the anesthetic exerts pharmacologic actions on other systems (Dipalma 1971, p. 196).

The absorption of an anesthetic from the injection site is dependent on the nature of the agent, the concentration, and the blood flow to the affected area. Mepivacaine, bupivacaine and lidocaine have similar absorption rates (Dipalma 1971, p. 196). Peak plasma concentrations of the drugs occur 15 to 30 minutes after injection. Mather,

Long and Thomas (1972) reported that the plasma half-lives of mepivacaine, bupivacaine, and lidocaine are 2.6 hours, 216 hours and 2.4 hours, respectively.

The nature of the absorptive surface varies with the different routes of administration. The local anesthetic procedures most commonly used in obstetrics include spinal block anethesia, lumbar epidural, pudendal, paracervical and local infiltration block anethesia. Spinal block anesthesia is accomplished by injecting a local anesthetic through the dura into the subarachnoid space of the lumbar area. Epidural anesthesia is produced by injection of a local anesthetic into the space surrounding the dura mater, with the spinal canal. Epidural and spinal blocks relieve pain during the first stage of labor and by an additional injection, analgesia can be extended into the second stage of labor. The paracervical block technique involves injection of the local anesthetic into each lateral fornix, or broad ligament, of the vagina. Paracervical blocks relieve the painful impulses from the first stage of labor. Pudendal blocks are performed by injecting a small amount of anesthetic transvaginally into the space between the sacrospinous ligament and the pudendal nerve. Because paracervical block anesthesia does not relieve pains from the second and third stage of labor, paracervical block is often combined with pudendal block anesthesia. Pudendal blocks do not relieve the discomforts caused by uterine contractions. Local anesthesia is accomplished by local infiltration at the episiotomy site (Greenhill and Briedman 1974, p. 284).

A number if investigators have measured blood levels of local anesthetics following regional anesthesia. Local anesthetics were rapidly absorbed from injection sites into the systemic circulation. Maternal levels tended to be higher following paracervical blocks as compared to lumbar epidural blocks, despite the fact that the total dose was usually lower for a paracervical block (Shnider and Way 1968b).

The popularity of paracervical block has generated interest in the speed of drug absorption from the broad ligament. Using atropine as a test agent, Burchell and Swasdio (1969) compared the speed of absorption from the broad ligament with other routes of administration (intravenous, subcutaneous, intramuscular). The speed of absorption from the broad ligament was close to the intravenous route.

Shnider and Way (1968a) reported that local anesthetics were absorbed from the sites of injection within 3-5 minutes. Upon injection and subsequent absorption, the amide local anesthetics had little difficulty penetrating membrane barriers, including the placenta.

The distribution to other tissues of a local anesthetic is determined by parameters such as the lipid/water partition coefficient, degree of ionization of the drug and the concentration of the free drug in the plasma. Katz (1968) studied the physiologic distribution of radioactively labeled lidocaine after intravenous injection into rats. The study indicated that plasma levels decreased rapidly, and after one minute only 6.8% of the injected dose remained in the circulation. The drug showed an affinity for highly perfused organs such as the liver, kidney and heart. Radiographic studies indicated that mepivacaine was distributed to tissues in a pattern similar to that of lidocaine

(Kristerson, Hoffman and Hansson 1965). The data indicated that the highest concentration occurred in excretory organs such as the kidney, urinary bladder, liver and gall bladder. Finster et al. (1973) reported that a relatively high level of lidocaine was found in the fetal heart. It was postulated that the high level of the drug in the heart could explain the susceptibility of the fetus to local anesthetics given to the mother.

The binding of drugs to proteins in the plasma can alter a local anesthetic's distribution. Tucker et al. (1970) measured the extent of binding of mepivacaine, lidocaine and bupivacaine to plasma proteins in normal male volunteers by ultrafiltration. For a local anesthetic at a concentration of 5 μg/ml, the extents of binding for bupivacaine, mepivacaine and lidocaine were 85%, 66% and 51%, respectively. Since the concentration of free mepivacaine or lidocaine in plasma was higher than that of bupivacaine, mepivacaine and lidocaine diffuse into the tissues more quickly than bupivacaine.

Hollmen (1973) compared the myocardial and cerebral uptake of bupivacaine to that of lidocaine in rabbits. The maternal heart-blood ratio of lidocaine, at equilibrium, did not differ from the heart-blood ratio of bupivacaine. However, the level of lidocaine did not equilibrate for 6 minutes. Two minutes following the injection of lidocaine, the maternal-heart blood ratio was 2.1. In the animals tested with bupivacaine the ratio was constant over time, at 1.03.

The fetal tissue-blood ratios of lidocaine and bupivacaine were constant over time. The mean fetal heart-blood ratio of bupivacaine was 0.50. The fetal heart-blood ratio of lidocaine was twice

as high as the heart-blood ratio of bupivacaine. The fetal brain-blood ratio of bupivacaine and lidocaine were 0.43 and 1.03, respectively (Hollmen 1973).

Placental Transfer

Studies in animals (Hollmen 1973) and in humans (Asling et al. 1970; Shnider and Way 1968a) have established that the amide local anesthetics undergo rapid placental transfer. Shnider and Way (1968a) reported that lidocaine appeared in the fetal circulation within two minutes of intravenous administration in humans.

Placental transfer is controlled by the same variables that determine a drug's distribution. Mepivacaine and lidocaine undergo placental transfer to a greater extent than bupivacaine. This is largely a consequence of greater binding of bupivacaine to plasma proteins. After intravenous administration of radioactively labeled local anesthetics to pregnant rabbits, Hollmen (1973) reported that the fetal-maternal ratio of lidocaine was higher than the fetal-maternal plasma ratio of bupivacaine (0.40).

In clinical studies, similar trends have been reported. After epidural anesthesia, Lurie and Weiss (1970) determined the fetal and maternal blood levels of mepivacaine and lidocaine. The fetal-maternal ratios of mepivacaine and lidocaine were, respectively, 0.73 and 0.70. In a recent study, the fetal-maternal ratio of bupivacaine was found to be 0.24, significantly lower than the values for mepivacaine and lidocaine. The lower fetal-maternal ratio of bupivacaine was accompanied by lower maternal plasma concentrations. As far as the neonate

is concerned, the favorable fetal-maternal ratio and lower levels suggest that bupivacaine is the safer local anesthetic agent (Belfrage, Berlin, Linstedt and Raabe 1973).

Cases in which the fetal-maternal ratio of a local anesthetic was greater than 1.0 have been reported (Shnider and Way 1968b; Asling et al. 1970). These cases involved paracervical injection. It was suggested that the drug reached the placenta by the uterine arteries. In this situation, the level of anesthetic in the intervillouw blood pool at the placenta would exceed the maternal branchial plasma level, and a high fetal plasma level would result.

Evidence indicates that the placenta possesses a high back-diffusion capacity. The placental transfer mechanism can clear local anesthetics from the fetal circulation. Morishima and Adamsons (1967) studies the placental clearance of mepivacaine following direct injection into guinea pig fetuses. The fetus in utero was tolerant to seemingly fetal doses of mepivacaine. This was due to the rapid transfer of the drug to the mother. If delivery occurs soon after administration of the agent to the fetus an important route of detoxification is removed and the burden of elimination is imposed on the neonate's own poorly developed detoxifying mechanisms.

Metabolism and Excretion

The metabolism of local anesthetics has been investigated in animals and in man. The most common metabolic pathways of lidocaine, mepivacaine and bupivacaine are N-dealkylation and aromatic hydroxylation followed by conjugation (Reynolds 1971; Thomas and Meffin 1972).

The proposed metabolic pathways for mepivacaine, lidocaine and bupivacaine are summarized on Figures 2, 3, and 4, respectively. Some of the metabolic pathways are not seen in the neonate, because the neonate is deficient in some of the drug metabolizing enzymes (Thomas and Meffin 1972).

Mepivacaine

In animals, the major route of mepivacaine metabolism is aromatic hydroxylation (Hansson, Hoffman and Kristerson 1965; Thomas and Meffin 1972). The studies by Thomas and Meffin indicated that in rats, 50% of the dose was converted to the 3' phenolic metabolite (metabolite 4), but Thomas and Meffin (1972) did not find evidence for this metabolite.

Thomas and Meffin (1972) reported that mepivacaine metabolism in humans differed from metabolism in rats. Aromatic hydroxylation occurred in the 3' and 4' positions of the aromatic ring, and equal portions of these metabolites (3 and 4) were formed. Formation of metabolite 2, the N-demethylated metabolite, accounted for approximately 2% of the dose. Metabolites 2, 3, and 4 represented 50% of the dose of mepivacaine. Meffin, Robertson et al. (1973) examined the urine of normal male volunteers for non-basic metabolites. Oxidation of the piperidine ring (metabolite 5) accounted for an additional 10% of the dose.

It has been established that neonates are deficient in the aromatic hydroxylation metabolic pathways (Gordon 1968). Meffin, Long and Thomas (1972) studied the elimination of basic metabolites of

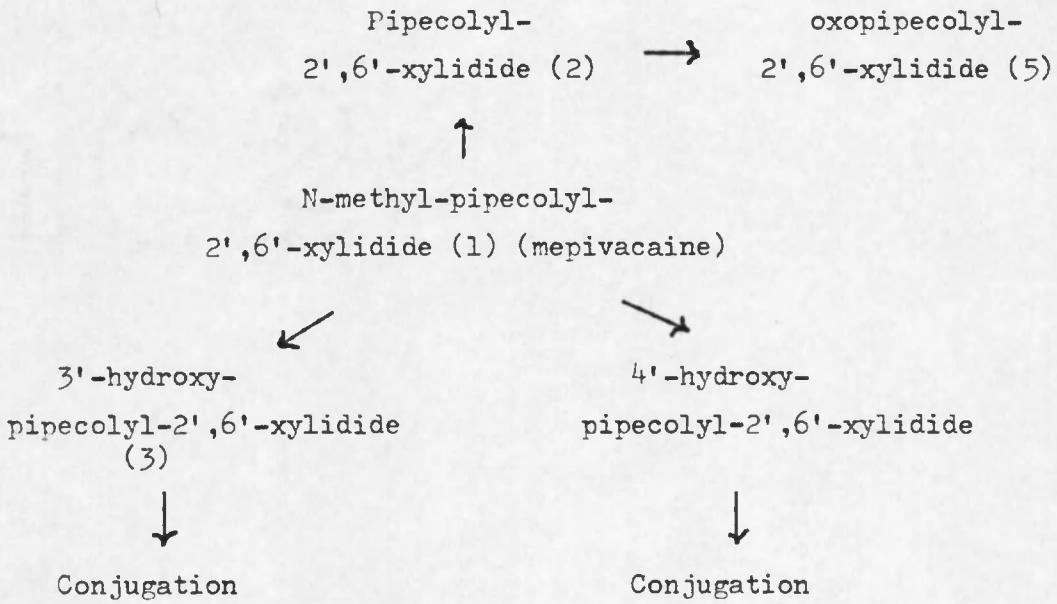


Figure 2. Flow diagram of mepivacaine metabolic pathways.

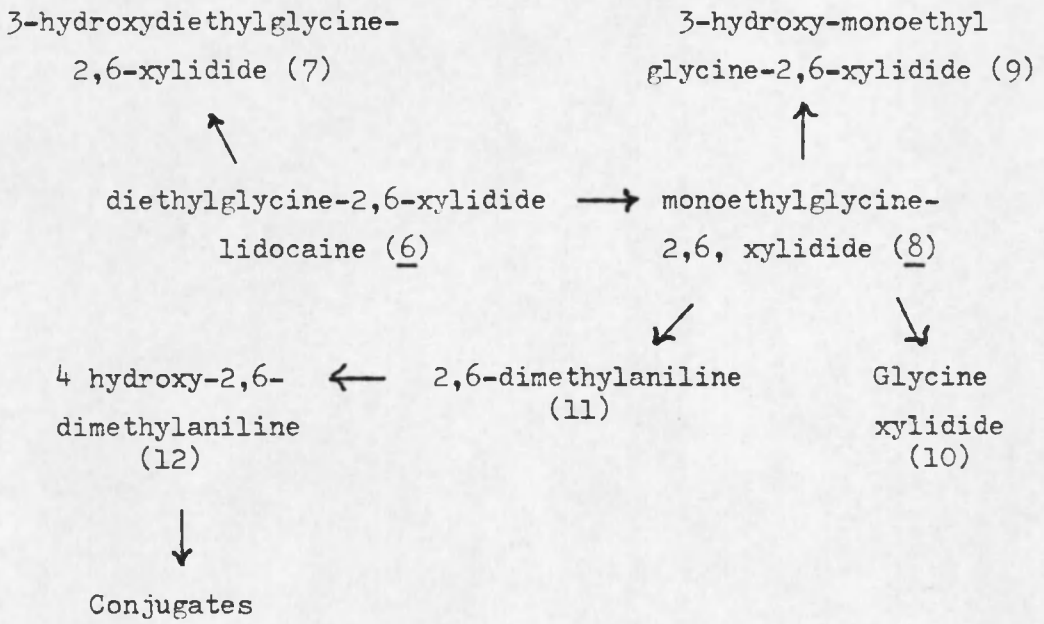


Figure 3. Diagram of lidocaine metabolic pathways.

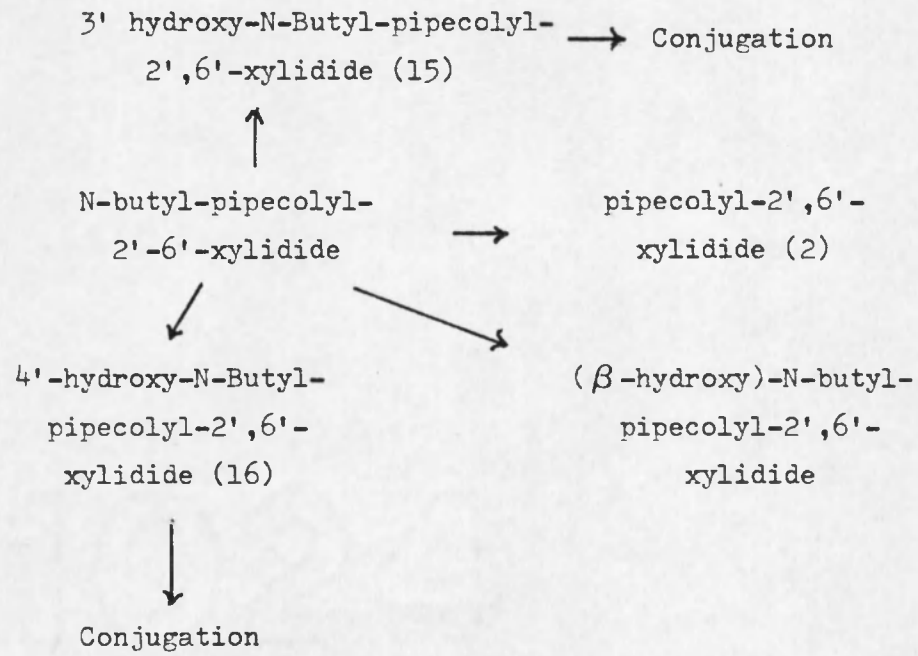


Figure 4. Flow diagram of bupivacaine metabolic pathways.

mepivacaine in maternal and neonatal urine. The results indicated that the neonates excreted extremely small quantities of metabolites 3 and 4. Metabolite 2 was recovered in maternal and neonatal urine. The ratio of 2 to intact mepivacaine was 0.32 in neonates and 0.63 in adults.

There was some question as to whether the metabolites were formed by the neonate or by the mother, and the metabolites transferred across the placenta. Since the neonate excreted only trace quantities of phenolic metabolites as glucuronide conjugates, metabolites 3 and 4 were probably formed by the mother. After placental transfer, conjugation occurred. Glucuronide conjugates do not undergo placental transfer. It would not be possible to determine whether N-demethylation can occur in the fetus. It has been proven that metabolite 2 is able to cross the placenta. Without direct administration of mepivacaine to the neonate, it would be impossible to determine whether the neonate can form 2 (Meffin, Long and Thomas 1972).

Although the activities of the metabolic pathways for mepivacaine are reduced in the neonate, it was shown that the neonate is able to eliminate mepivacaine within 30 hours. An increased rate of renal excretion of unchanged mepivacaine compensates for reduced metabolism in the neonate (Meffin, Long and Thomas 1972).

Lidocaine

The metabolism of lidocaine has been studied in animals and in man. Evidence indicates that the diethyl amino group of the lidocaine molecule is metabolically more labile than the N-methyl group of

the mepivacaine molecule (Thomas and Meffin 1972). The major metabolic pathway appears to be N-dealkylation followed by secondary oxidations, conjugations and hydrolyses. After studies of radioactively labeled lidocaine in rats, Keenaghan and Boyes (1972) reported that 73% of the dose was converted to metabolite 12. Only 0.2% of the dose was recovered as intact lidocaine. Using isolated rat liver cells, Nyberg et al. (1977) found that lidocaine was de-ethylated rapidly, Metabolite 8 was metabolized further before leaving the liver cell.

Strong and Atkinson (1972) determined the plasma concentrations of lidocaine and metabolite 8 in man after intravenous administration of lidocaine. The plasma concentration of 8 was about one tenth the concentration of lidocaine. Metabolite 8 has been associated with toxic side in cardiac patients treated with lidocaine (Beckett, Boyes and Appleton 1966). The formation of 8 has been disputed in other studies, however. After oral administration of lidocaine to human volunteers, Nelson et al. (1977) isolated the metabolites of lidocaine and confirmed their identity by chemical ionization mass spectrometry. The major metabolite was 12. Metabolite 8 was not detected in this study. Metabolism studies of lidocaine in the neonate have not been reported.

Shnider and Way (1968b) studied the metabolism of lidocaine in placental tissue. Placental tissue samples from 5 patients, whom had not received lidocaine, were homogenized, and incubated with lidocaine. The tissue was extracted and subjected to gas chromatography. There was no evidence of metabolism of lidocaine by the placenta.

Bupivacaine

Reynolds (1971) compared bupivacaine metabolism to mepivacaine metabolism in man. The major metabolite in both anesthetics was 2. Bupivacaine was converted to 2 at a faster rate for the first two hours after administration. After that point, mepivacaine and bupivacaine were converted to 2 at similar rates. Over a 24 hour observation period, the amount of 2 and intact bupivacaine excreted in the urine represented, respectively, 5% and 6% of the dose. Three additional metabolites of bupivacaine, 5, 6 and 7, were isolated from the urine of rabbits, and identified by mass spectrometry (Bouche and Lhoest 1976).

Belfrage, Berlin, Raabe and Thalme (1975) studied the decline of bupivacaine in maternal and neonatal blood for 20 hours following delivery. In most cases, the umbilical drug concentrations at birth were 25% of the corresponding maternal values. The rates of drug blood level declines were similar in the mother and the neonate. The maternal half life of bupivacaine was approximately 9 hours. As was stated previously, Mather, Long and Thomas (1972) reported a lower value for the plasma half life of bupivacaine. Belfrage, Berlin, Raabe and Thalme (1975) postulated that this discrepancy may have been due to the fact that Mather's investigation was conducted on normal male volunteers. The study by Belfrage, Berlin, Raabe and Thalme was conducted on newly delivered women who may have had abnormal liver functions. In addition, the investigation by mather, Long and Thomas was based on observations during an 8 hour period which could lead to an underestimation of the half life of the drug.

Toxicity

Local anesthetics are capable of blocking nerve conduction in the sensory and motor fibers, the ganglia, and portions of the central nervous system. A direct action on smooth muscle produce arteriolar dilation. Local anesthetics have a quinidine-like effect on the heart, reducing myocardial excitability and contractility. High blood levels can result in central nervous stimulation, causing cortical symptoms of excitement, disorientation, nausea and vomiting and convulsions (Goth 1976, p. 367).

Studies in humans have established threshold concentrations for objective signs of toxicity (Bromage and Robson 1961). Most investigators related venous blood levels to local anesthetic toxicity. Shnider and Way (1968b) postulated that arterial levels are a more important indicator of toxicity because the arterial plasma levels and the blood flow to the organs determine the level of the drugs in the brain and heart.

Most of the data on human toxicity of the local anesthetics are based on reports of the actual use of these drugs in obstetrics, but there are a few reports of toxicity studies in normal adults in the literature. Although these studies were conducted with intravenously infused local anesthetics, the data are relevant because all of these agents are absorbed into the circulation.

Shnider and Way (1968b) studied 57 women who received lidocaine for epidural, paracervical or pudendal anesthesia. The toxic threshold of lidocaine in maternal arterial plasma appeared to exceed 6 μg/ml. After epidural anesthesia using mepivacaine, Morishima et al. (1966)

reported that maternal symptoms of toxicity were associated with levels of mepivacaine exceeding 6.3 μg/ml. Foldes et al. (1960) reported that with a slow intravenous infusion of lidocaine, cerebral signs of toxicity (cortical irritation, muscular fasciculations) appeared at a venous plasma concentration of 5.3 μg/ml.

The toxic threshold of bupivacaine in obstetrics has not been reported in cases of obstetrical use of the drug. There are reports of severe maternal bupivacaine toxicity in the literature, but blood levels of the drug were not measured in these cases (Philip and Brown 1976; Ryan 1973). Jorfeldt et al. (1968) measured plasma levels of bupivacaine in adult male volunteers. A dose of 1.25 mg/kg was administered by intravenous infusion over 20 minutes. The maximum venous plasma level recorded was 2.4 μg/ml but no signs of toxicity were observed. Reynolds (1971) reported that after intravenous infusion of 1.87 mg/kg over 90 minutes, one subject experienced wild inebriation at an arterial plasma level of 1.7 μg/m. In a second subject, paraesthesias in the fingers and tongue occurred at an arterial plasma concentration of 2.04 μg/ml and a venous plasma concentration of 1.5 μg/ml.

The symptoms of toxicity in adults are similar for mepivacaine, lidocaine and bupivacaine. In obstetric practice, the most common maternal signs of toxicity are those of centran nervous stimulation. Symptoms include apprehension, confusion, nausea and vomiting (Morishima et al. 1966). Major complications such a convulsions, loss of consciousness and circulatory collapse have occurred in cases of extreme intoxication (Philip and Brown 1976).

In some studies using mepivacaine or lidocaine, minimal maternal hypotension (30% below the control values of below 100 mg/hg) was observed in patients undergoing epidural anesthesia. The hypotension was relieved by left uterine displacement (Shnider and Gildea 1973). This hypotension did not appear to be related to the dose administered or to the blood concentration of the drug at birth (Morishima et al. 1966).

Signs of toxicity in the fetus have been observed when the concentration of mepivacaine and lidocaine were 3.0 μg/ml and 2.7 μg/ml, respectively (Teramo and Rajamaki 1971; Morishima et al. 1966). A value for the threshold of toxicity of bupivacaine in the fetus has not been reported. Fetal and neonatal toxicity are manifested by bradycarida, tachycardia and acidosis. In cases of severe intoxication, hypotonia, convulsions and death can occur. In most instances, the only recognized symptom of fetal toxicity is fetal bradycardia. It has been shown that a significant number of patients who developed fetal bradycardia later had low Apgar Scores (Shnider and Gildea 1973).

The reported incidence of fetal bradycardia following paracervical block ranged between 3% and 50%. The results of most studies agreed with those of Shnider and Gildea (1973), in which the reported incidence of bradycardia was approximately 20%. These data may have a low bias. The incidence reported by Shnider and Gildea (1973), Baskett and Carson (1974) and Shnider et al. (1970) did not rely upon continuous monitoring of the fetal heart rate. In studies in which the fetal heart rate was monitored continuously (Asling et al. 1970; Liston, Adjepon-Yamoah and Scott 1973), the reported incidence of

fetal bradycardia was somewhat higher. Liston (Liston et al. 1973) detected fetal tachycardia in 33% of the cases studied, in addition to a 33% incidence of fetal bradycardia. Teramo and Rajamaki (1971) reported a 50% incidence of fetal bradycardia. Teramo and Rajamaki's results could be due to the relatively high dose of mepivacaine, 400 mg, that was administered. In studies reporting a lower incidence of bradycardia, the dose rarely exceeded 200 mg. Correlations between the severity of fetal bradycardia and fetal acidosis have been demonstrated (Teramo and Rajamaki 1971; Liston et al. 1973; Asling et al. 1970). Studies evaluating the association between paracervical block and fetal bradycardia are summarized in Table 1.

Shnider et al. (1970) presented statistical evidence that factors such as maternal premedication before the block, fetal position, or the condition of fetal membranes at the time of block presented no significant predisposition to fetal heart rate abnormalities. The study also showed that there was no significant difference between mepivacaine and lidocaine concerning the incidence of bradycardia. The data did show that a significantly increased incidence of fetal heart rate abnormalities was associated with pre-existing fetal distress.

Paracervical block anesthesia has been associated with infant mortality when infants have been injected during the attempted block (Finster et al. 1965; Sinclair et al. 1965). Apnea, bradycardia, hypotonia and convulsions in an infant delivered by a mother who had received paracervical block anesthesia would indicate that the infant may have been inadvertently injected with the agent. Dodson, Hillman

Table 1. List of the reported incidence of fetal bradycardia following paracervical block anesthesia and whether or not continuous monitoring was used.

Author	No. of Patients	Local Anesthetic	Incidence of Fetal Bradycardia	Continuous Heat Rate Monitoring
Shnider et al. 1970	845	Lidocaine	19%	no
		Mepivacaine	20%	no
Shnider and Gildea 1973	1839	Mepivacaine	22%	no
		Lidocaine	22%	no
Teramo and Rajamaki 1971	12	Mepivacaine	50%	yes
Liston et al. 1973	12	Lidocaine	33%	yes
Asling et al. 1970	17	Mepivacaine	41%	yes
Gordon 1968	150	Mepivacaine		no
Yates 1969	95	Mepivacaine	12%	no
		Lidocaine	14%	
		Bupivacaine	10%	
Baskett and Carson 1974		Bupivacaine	3.2%	no

and Hillman (1975) studied the tissue distribution and plasma concentration of mepivacaine in a fatal case of neonatal mepivacaine poisoning. The serum levels were somewhat lower than those in other fatal cases of mepivacaine poisoning (Finster et al. 1965). However, the levels detected in the central nervous system were high. The pre-exchange serum concentration of mepivacaine was 15.4 μg/ml, while the cerebrospinal (CSF) fluid level was 13 μg/ml.

Rosefsky and Petersiel (1968) reported two cases of perinatal death in which there was no evidence of accidental injection of a local anesthetic into either fetus. These cases occurred after attempted caudal block anesthesia, using mepivacaine. One infant was still born; the other survived for 45 hours. The concentration of mepivacaine in the urine at 36 hours was 6.2 μg/ml; at the time of death it was 0.75 μg/ml. Rosefsky and Petersiel postulated that the drug was absorbed rapidly by the fetus via the uterine arteries.

Epidural anesthesia results in lower maternal and fetal blood levels. This would indicate that epidural blocks are of lower potential danger to the fetus (Shnider and Way 1968b). Besides the difference in vascularity between the paracervical and the epidiral region, a likely reason for lower blood levels of anesthetic after epidural blocks would be that the time of injection is further from delivery in the epidural series, thereby allowing the placenta to clear the drug from the fetus. Morishima et al. (1966) studied the consequences of placental transfer of mepivacaine following epidural block anesthesia. There was a 21% incidence of neonatal depression, or 12 of 56 cases. It should be noted, however, that in 5 of the cases, the

mothers had received over 600 mg of mepivacaine in 2½ hours of continuous lumbar or caudal anesthesia.

In one study lumbar epidural anesthesia with bupivacaine was administered to 33 women (Belfrage, Berlin, Raabe and Thalme 1975). No signs of toxicity were reported in any mother, although there was one case of fetal tachycardia. The umbilical artery concentration of bupivacaine at delivery was 0.051 μg/ml. The mean maternal level at delivery was 0.18 μg/ml. The mean Apgar Scores at one minute and five minutes were, respectively, 8.3 and 9.9. It is claimed that the lower dose necessary for analgesia and the low amount transferred to the fetus make bupivacaine a more suitable local anesthetic than mepivacaine or lidacaine.

Methods of Evaluation

Clinical Assessment

The clinical condition of the neonate is regarded as an approximation of the infant's reaction to the local anesthetic. Routinely, the Apgar Score is used to assess the condition of the infant. The Apgar Score is a subjective evaluation of the neonate's pulse, respiration, color, tone and reflex irritability (Greenhill and Briedman 1974, p. 693). Some bias is introduced by obstetricians who consistently overestimate the scores. It is not possible to determine the potential neurological effects of the local anesthetics by the Apgar Score alone (Scanlon, Brown, Weiss and Alper 1974). In recent years, studies have demonstrated subtle behavioral changes in neonates whose mothers had received various sedatives, analgesics or anesthetics during labor.

A new dimension has been added to neonatal evaluation procedures with the standardization of neurobehavioral tests. The examination involves an assessment of the neonate's state of wakefulness, various reflexes, muscle tone, and responses to various stimuli. Scanlon, Brown et al. (1974) performed these neurobehavioral tests on 41 infants, 28 whose mothers had received continuous epidural blocks with either lidocaine or mepivacaine. Although the mean umbilical concentrations of local anesthetics were well below the toxic threshold, scores of muscle strength and tone in the epidural group infants were significantly lower than those of infants in the non-epidural group. By traditional evaluations, all of the infants appeared to be normal.

Infants whose mothers had received bupivacaine for epidural block anesthesia were subjected to neurobehavioral evaluation tests. Although infants whose mothers received mepivacaine had shown poor performance on these tests (Scanlon, Brown et al. 1974), neonates whose mothers received bupivacaine had normal or superior scores on tests of muscle strength and tone. It was postulated that the improved performance of this group of infants was due to lower fetal absorption of bupivacaine, relative to mepivacaine or lidocaine. The mean umbilical concentration of bupivacaine at birth was 0.1 μg/ml (Scanlon, Ostheimer, et al. 1976).

The condition of the fetus in utero can be evaluated by monitoring the fetal acid/base balance and the fetal heart rate. It has been emphasized that the fetal heart beat must be monitored continuously (Baskett and Carson 1974). That the protocols of some studies used only occasional monitoring would explain the conflicting

values for the incidence of fetal bradycardia that are in the literature. Measurement of fetal acid/base balance is accomplished by obtaining fetal scalp blood specimens. Sample collection is the main difficulty. The possibility of contamination by amnionic fluid or by room air must also be recognized.

Analytical Methodology

The literature indicates that a variety of analytical procedures can be used to estimate the concentration of local anesthetics in biological fluids. A number of studies relied upon a colorimetric method based upon the formation of a salt by methyl orange (Sung and Truant 1954). Since a number of organic bases react with methyl orange, the specificity of this procedure is questionable. This might explain the high levels of local anesthetic after paracervical anesthesia reported by Gordon (1968).

Daniel and Morishima (1967) included an extraction step which increased the specificity of this method. The modification included back-extraction into acid. It was assumed that organic bases of lower molecular weight would be eliminated at this point. However, molecular weight differences between the unchanged anesthetic molecule and its metabolite may not be sufficient to allow separation by this means.

The authors should have indicated whether the method was specific for the intact local anesthetic in the presence of metabolites. A drug free plasma fortified with a local anesthetic metabolite should have been analyzed by the methyl orange method. To show a lack of

interference by the metabolite would verify the specificity of this method.

There are more than a dozen gas chromatographic methods for detection of mepivacaine, lidocaine, and bupivacaine in the literature. Most of the methods utilize flame detection of the anesthetics. Thomas and Meffin (1972) described chromatography conditions which would separate intact mepivacaine and lidocaine from their respective metabolites. Edhorn (1971) published a paper which described an extraction procedure for lidocaine in whole blood. Edhorn stressed the major obstacles to successful chromatography of blood samples by describing the origin of extraneous peaks, and the proper ways to avoid them. Berlin, Persson and Belfrage (1973) described a micro method for determining bupivacaine from plasma. Hucker and Stauffer (1976) described a sensitive gas chromatographic method for analyzing lidocaine in plasma, using a nitrogen-sensitive detector. The detector afforded sensitivity and specificity such that samples could be injected after a single extraction step. Local anesthetics and their metabolites have been quantitated by mass spectrometry (Nelson et al. 1977). This method, in addition to allowing a sensitive detection method, also provided a rigorous criteria for compound identification.

Statement of the Problem

It was felt that there was a significant incidence of detectable blood levels of local anesthetics in normal obstetric practice. To date, there have been no determinations of the incidence of detectable blood levels of these agents in a large sampling of neonates in routine obstetric practice.

A gas chromatographic method was developed for the determination of mepivacaine and lidocaine in neonatal cord blood. It was necessary for the method to be sensitive, reproducible, and easily modified to accommodate small sample sizes.

One hundred cord blood samples were obtained from each of two hospitals: The Arizona Health Sciences Center and Tucson Medical Center, and analyzed for the presence of local anesthetics.

The charts of the Arizona Health Sciences Center cases were reviewed and pertinent clinical data were recorded. The clinical data and the analytical data were combined and possible correlations were evaluated statistically. Of particular interest were the relationship between the analytical data, the route of administration and the Apgar Score. Clinical data from Tucson Medical Center were not reviewed, because the patients' charts were not available.

Evaluation of the amnionic fluid is an important method of intrauterine diagnosis. Often, infiltration with a local anesthetic is incorporated into the amniocentesis procedure. It was of interest to determine whether there were any detectable levels of local anesthetic in the amnionic fluid. Specimens were obtained from the Arizona Health Sciences Center, and analyzed for presence of the agents.

Two cases of obvious mepivacaine toxicity were encountered at the Arizona Health Sciences Center. Samples of urine, blood and gastric aspirates were obtained and tested for the presence of mepivacaine. It was of interest to determine whether the analytical method could be applied to these specimens. The cases also offered an opportunity to study the elimination of mepivacaine in the neonate.

EXPERIMENTAL

Method A

Materials

Carbocaine® was purchased from Wintrop. Carbocaine is an aqueous solution of mepivacaine hydrochloride and methyl paraben, a preservative. Mepivacaine was isolated from the injection preparation by the following procedure. Ten (10) ml of Carbocaine were shaken with three -50 ml portions of ether to remove the preservative. After the ether phase was discarded, the aqueous layer was made basic with IN NaOH and the mepivacaine was extracted with three -50 ml portions of ether. The ether fractions were combined and evaporated. The melting point of the precipitate (149-153°) was used to determine the purity of the recovered product. A stock solution of 2.5 μg/ml was prepared in freshly distilled ether.

Narcaine® was purchased from Wintrop. Narcaine is an aqueous solution of bupivacaine hydrochloride and methyl paraben. Five (5) ml of Narcaine were shaken with three -25 ml portions of ether to remove the preservative. The aqueous layer was made basic with IN NaOH, then the bupivacaine was extracted with three -20 ml portions of ether. The ether was evaporated, and the melting point of the recovered precipitate was measured (107-108°). An internal standard solution was prepared in freshly distilled ether (1 μg/ml).

The ethyl ether used in the study was analytical reagent grade (Mallinckrodt) and the carbon disulfide used was chromatographic grade (Analabs).

Procedure

The gas chromatography columns were rinsed with dilute hydrochloric acid, followed by distilled deionized water, organic solvents, and carbon disulfide. The columns were dried with a stream of nitrogen and filled with a solution of 5% dimethyl dichlorosilane (Supelco) in toluene. After one minute, the columns were emptied and rinsed with toluene followed by methanol. After the columns were dried with a stream of nitrogen, they were ready to be packed. The packing, 3% OV 225 on 80/100 mesh Gas Chrom Q (Applied Science, Inc.), was prepared by a pan coated method (McNair and Bonelli 1968, p. 64). The columns were packed with stationary phase, and conditioned at 250° overnight.

Consent forms were obtained from the mothers upon admission. Neonatal cord blood samples were routinely collected at delivery, and refrigerated in the Arizona Health Sciences Center Blood Bank for one week, for possible use. After a week they were discarded. Only samples which were to be discarded were received for the analysis of local anesthetics. Samples of amnionic fluid were collected for chromosome studies. After the amnionic cells were spun down and collected, the remaining fluid was analyzed for local anesthetic levels. Usually, this remaining fluid was discarded.

The cord blood samples were centrifuged (1500 RPM, 10 minutes), and the separated serum was transferred to a test tube. These samples

were refrigerated until analysis. The analysis procedure was a modification of the method published by Meffin, Long and Thomas (1972). One (1) ml of serum or biological fluid (urine or gastric aspirates), 1 ml of internal standard solution and 0.5 ml of 5N NaOH were mixed in a 50 ml test tube that was fitted with a teflon lined cap. The contents of the tube were extracted twice with 5 ml of ether by the following procedure. The tube was shaken for ten minutes on a mechanical shaker. After centrifugation (1500 RPM, 10 minutes), the ether layer was transferred to a 15 ml centrifuge tube. One (1) ml of 0.5 N HCl was added to the combined ether fractions, and the contents of the tube was shaken for ten minutes. After centrifugation, the ether layer was aspirated and discarded. The aqueous phase was made alkaline with 0.5 ml of 5 N NaOH, and extracted with ether (2 x 5 ml) by the procedure described above. The ether layers were combined in a 10 ml test tube, and the ether was evaporated to dryness under a stream of nitrogen. The tube was immersed in ice, and 0.2 ml of CS_2 was added to the residue. The sample was agitated using a vortex mixer (Vortex Genie), then 2 ul of this mixture was injected into the gas chromatograph. The procedure is summarized by the flow diagram on Figure 5.

Method B

Materials

Mepivacaine was isolated from Carbocaine by the procedure described in Method A. Lidocaine hydrochloride was donated by Dr. A. L. Picchioni of The University of Arizona Department of Pharmacology. A stock solution (2.0 μg/ml) was prepared in ether. Chlorpheniramine

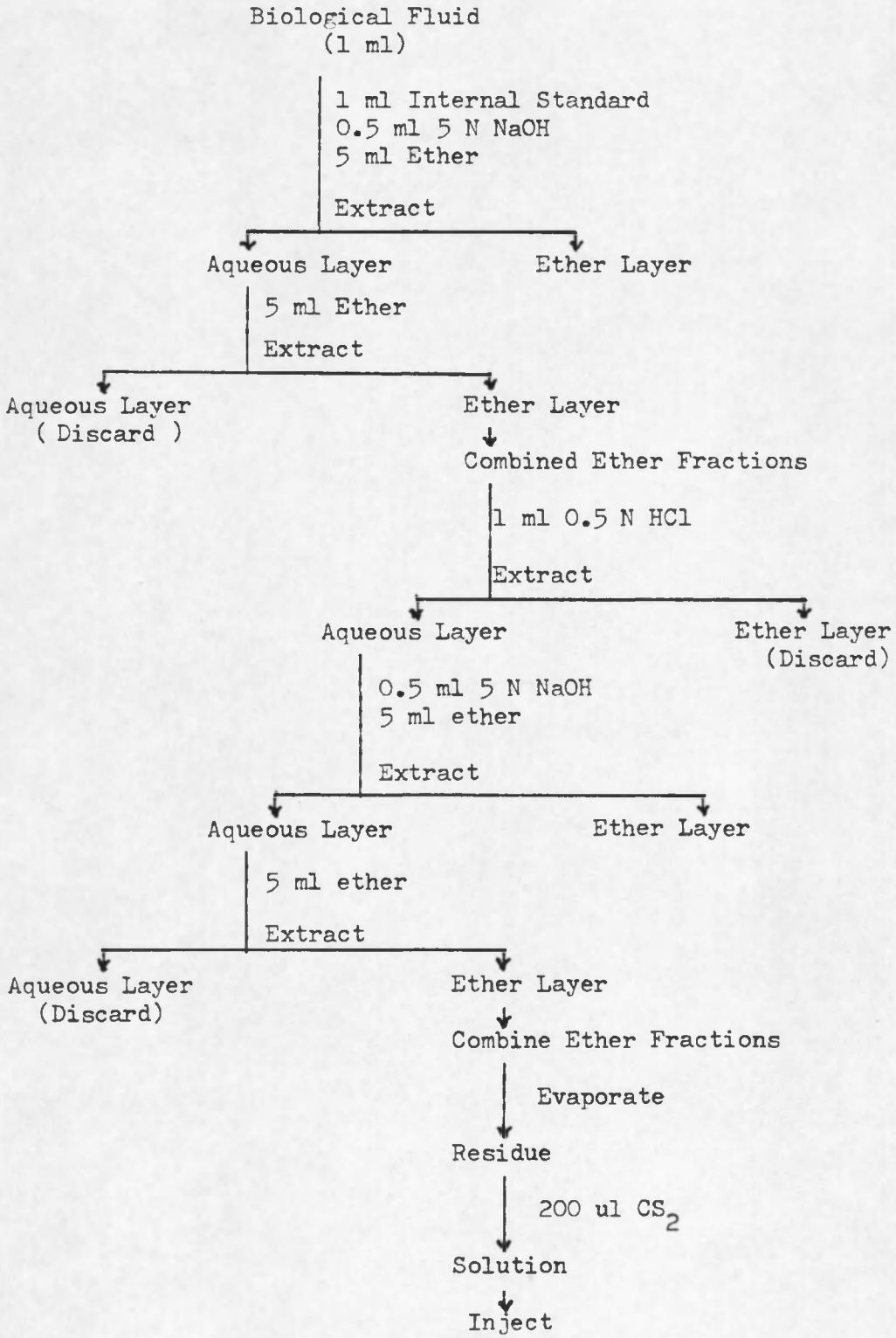


Figure 5. Flow diagram outlining Method A extraction procedures.

maleate was also donated by Dr. Picchioni. A stock solution (4.5 μg/ml) was prepared in distilled water. Deionized water was distilled over $KMnO_4$, and filtered immediately before use.

Procedure

All glassware used for this method was carefully cleaned to remove impurities that might cause chromatographic interference. The glassware was soaked in Alconox for at least one hour or preferably overnight and was scrubbed thoroughly. Then it was rinsed with dichromate cleaning solution, alcohol, tap water, and finally with distilled deionized water.

Immediately after the cord blood samples were released from the blood bank, they were centrifuged (1500 RPM, 10 minutes). The serum was recovered and frozen until analysis. One (1) ml of serum of biological fluid (urine, gastric aspirates, amnionic fluid) and 0.5 ml of 5N KOH were mixed in a 50 ml test tube that was fitted with a teflon lined cap. The mixture was extracted twice with 5 ml of freshly distilled ether. After the addition of 5 ml of ether, the mixture was shaken (10 minutes) and centrifuged (10 minutes, 1500 RPM). The ether layers were combined in a 15 ml glass stoppered centrifuge tube, and the volume of the recovered ether fraction was recorded. One (1) ml of 0.5 N HCl and 0.1 ml of chlorpheniramine maleate solution (4.5 μg/ml) were added, and the tube was agitated on a vortex mixer for 20 seconds. After centrifugation (10 minutes, 1500 RPM), the ether was aspirated and discarded. Any remaining ether was evaporated under a stream of nitrogen.

The aqueous phase was made basic with 0.5 ml of 5 N KOH, and 0.1 ml of CS_2 were added. The solution was agitated on a vortex mixer for ten seconds, and centrifuged at 2000 RPM for ten minutes, leaving a clear bubble of CS_2 at the bottom of the tube. The CS_2 layer was carefully sampled with a 10 µl syringe (Hamilton, Inc.) so that none of the aqueous layer was injected. One (1) to three microliters were injected into the gas chromatograph. This procedure is summarized by a flow diagram (Fig. 6).

Chromatography

Chromatography was performed using a Hewlett Packard Gas Chromatograph (Model 5700 A) with dual flame ionization detectors and dual fix foot, ¼ inch glass columns. Operating conditions were: oven temperature, 220°; nitrogen and hydrogen flow rates, 60 ml/min; air flow rate, 240 ml/min.

It was important that the syringe be kept free of contaminants. Immediately after injection, the syringe was rinsed with methanol, ether, and finally with carbon disulfide. If peak tailing became noticeable, 50 µl of 5% dichlorodimethylsilane (Supelco Co.) in toluene was injected. Before silane treatment, the column was disconnected from the detector, and after the treatment was conditioned at 260° (detector, 300°) overnight.

Calculations

For Method A, anesthetic levels were quantitated by reference to bupivacaine, the internal standard. A known amount of the internal standard was added to each sample before extraction, and the peak area

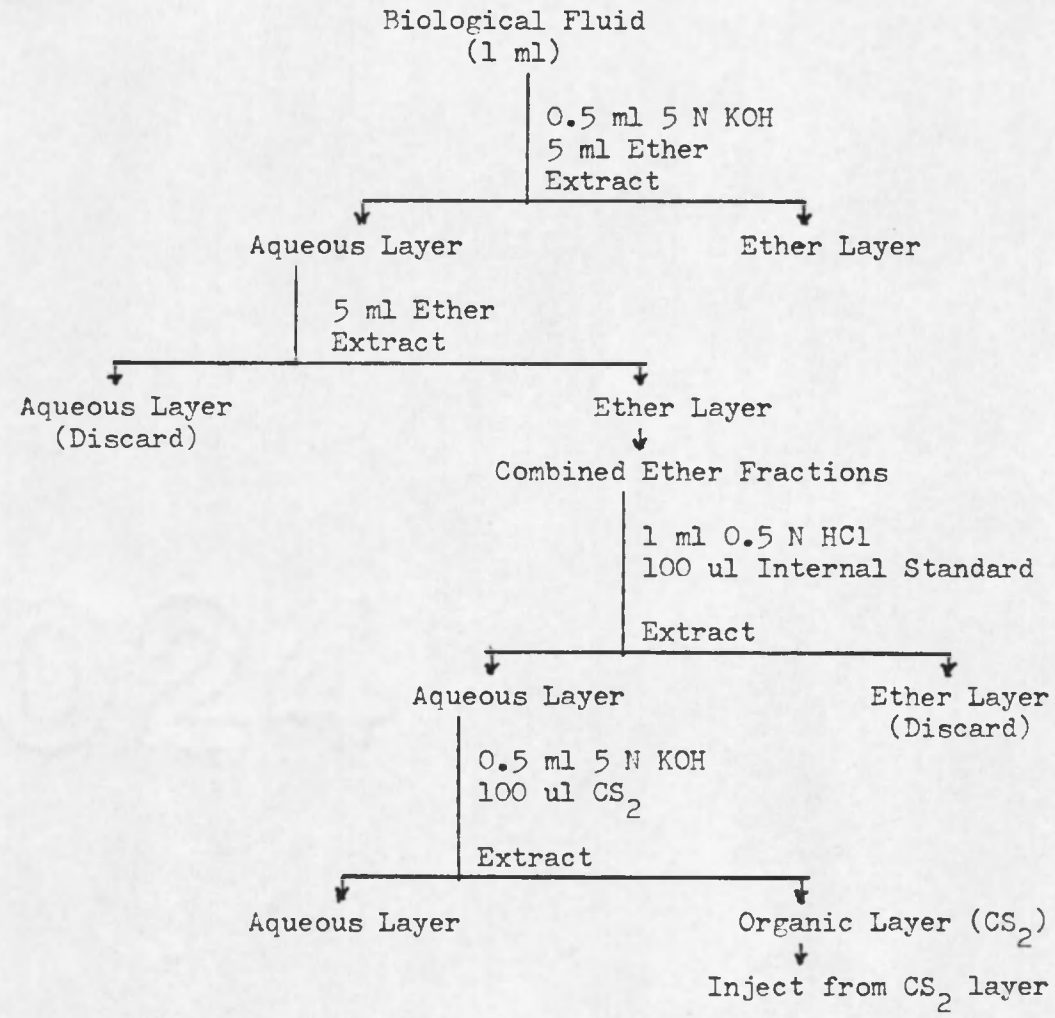


Figure 6. Flow diagram outlining Method B extraction procedures.

ratios were calculated from the resulting chromatograms. Calibration plots were prepared by fortifying separate drug-free plasma samples with known amounts of mepivacaine. Values for m, the slope, and b, the y-intercept, were calculated from the calibration plot using the method of least squares. The levels of mepivacaine in the samples were calculated using the following equation:

$$C_a = \frac{1}{m}\left(\frac{A_a}{A_b} \times \frac{w_b}{v_s} - b\right)$$

where: C_a the concentration of the local anesthetic (mepivacaine, μl/ml)

$\frac{A_a}{A_b}$ the peak area ratio between the local anesthetic and the internal standard peaks

w_b the weight of internal standard added (μg)

v_s the volume of the sample (ml)

For Method B, mepivacaine and lidocaine levels were quantitated by reference to chlorpheniramine maleate, the internal standard. After the serum was extracted with ether, a known amount of internal standard was added to the combined ether fractions. The calculation was adjusted according to the volume of the recovered ether fraction.

$$C_a = \frac{1}{m}\left(\frac{A_a}{A_c} \times \frac{w_c}{V_R/10} \times \frac{1}{v_s} - b\right)$$

where: C_a the concentration of the local anesthetic (mepivacaine or lidocaine, μg/ml)

$\frac{A_a}{A_c}$ the peak area ratio between the local anesthetic and the chlorpheniramine maleate peaks

w_c the weight of chlorpheniramine maleate added (μg)

V_R volume of ether fractions recovered (ml)

v_s the volume of the sample (ml)

Stability Study

A stability study was performed to determine the extent to which the specimens decomposed before they were released by the blood bank. Methanolic solutions of lidocaine and mepivacaine were added to separate 10 ml samples of whole blood. Each fortified blood sample was immediately divided into ten portions, transferred to separate test tubes, and sealed with parafilm. The samples were refrigerated, and samples were removed at various times in the next ten days. The serum was recovered and transferred to a clean test tube, where it was frozen until analysis. All the samples were analyzed on the same day, using analytical procedure B.

RESULTS

Analytical Methodology

A flame gas chromatographic method using similar chromatographic conditions to those described by Thomas and Meffin (1972) was used to detect mepivacaine and lidocaine in biological fluids. During the course of this project, two extraction procedures were developed for the serum samples.

Method A determined the concentration of mepivacaine in biological fluids. Bupivacaine was added as an internal standard. The serum sample was made alkaline to convert the local anesthetic to its unionized form, and extracted with ether. The drug was converted to the water soluble hydrochloride salt by addition of dilute acid. The sample was washed with ether to remove the lipid components of the serum sample. The aqueous phase was alkalinized to convert the anesthetic to its lipophilic form. The anesthetic was extracted with ether. After the ether was evaporated, the residue was reconstituted in carbon disulfide and chromatographed. The retention times of mepivacaine and bupivacaine were 7.9 minutes and 9.4 minutes, respectively. Figure 7 illustrates a typical chromatogram obtained from this procedure. The slope, y intercept, lower limit of detection and correlation coefficient of Method A are listed on Table 2.

Method B was capable of quantitating mepivacaine and lidocaine in biological fluids. Chlorpheniramine maleate was added as the

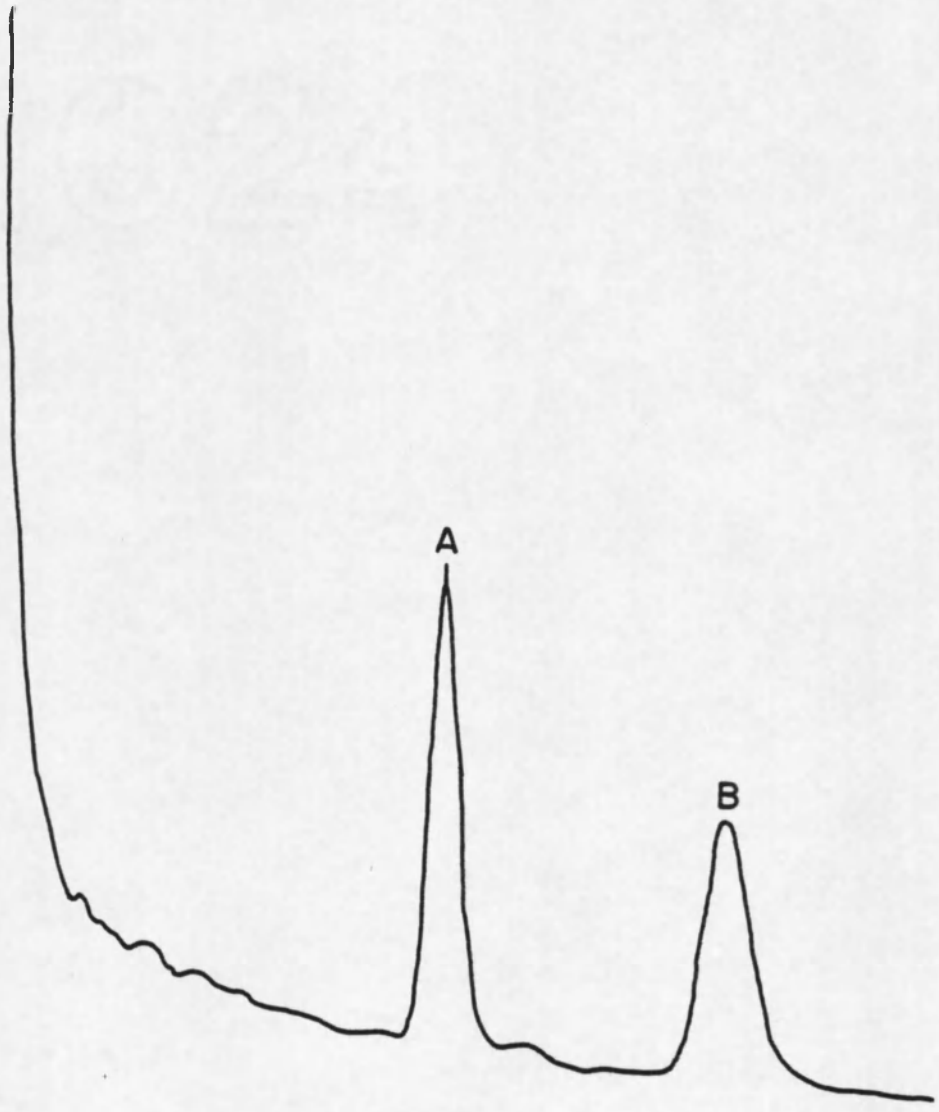


Figure 7. Gas chromatogram of a plasma sample containing mepivacaine, processed by Method A. -- Gas chromatogram of mepivacaine and internal standard (bupivacaine) extracted from plasma by Method A. Key: A, mepivacaine; B, bupivacaine.

Table 2. Statistical data of the analytical procedures.

Parameter	Method A, Mepivacaine	Method B, Mepivacaine	Method B, Lidocaine
Slope	0.48746	0.93319	1.27504
y-Intercept	-.02403	-.01033	-.00451
Correlation coefficient (R)	0.99761	0.99980	0.99715
Standard error of regression	0.177	0.0220	0.0284
Lower limit of detection	0.4 µg/ml	0.9 µg/ml	0.15 µg/ml

internal standard. The serum sample was made alkaline to convert the anesthetic to its unionized form, and extracted with ether. The ether extract was acidified to convert the drug to its water soluble hydrochloride salt. The sample was washed with ether to remove the lipophilic components of the serum. The aqueous layer was made alkaline, and the local anesthetic was extracted into carbon disulfide by direct addition of the solvent to the aqueous phase. A portion of the carbon disulfide layer was injected into the gas chromatograph. The retention times of chlorpheniramine maleate, lidocaine and mepivacaine were 3.0 minutes, 3.6 minutes and 7.9 minutes, respectively (Figs. 8 and 9). The slope, y intercept, lower limit of detection and correlation coefficients of Method B are listed on Table 2. These data indicate that Method A and Method B possess similar linearity.

Stability Profiles

The stability study indicated that both mepivacaine and lidocaine decomposed when the whole blood samples were refrigerated. The stability data was used to calculate equations for the rate of decomposition of mepivacaine and lidocaine using the method of least squares. The decomposition of mepivacaine was a straight line with a correlation coefficient of 0.95685 (Fig. 10). The concentration of mepivacaine after ten days was 47% that of the control sample. There were no extraneous peaks in the sample chromatograms. For lidocaine, the decomposition also fit a straight line with a correlation coefficient of 0.99845 (Fig. 11) and the concentration after ten days was 65% that of the control sample. There were no extraneous peaks in the sample chromatograms.

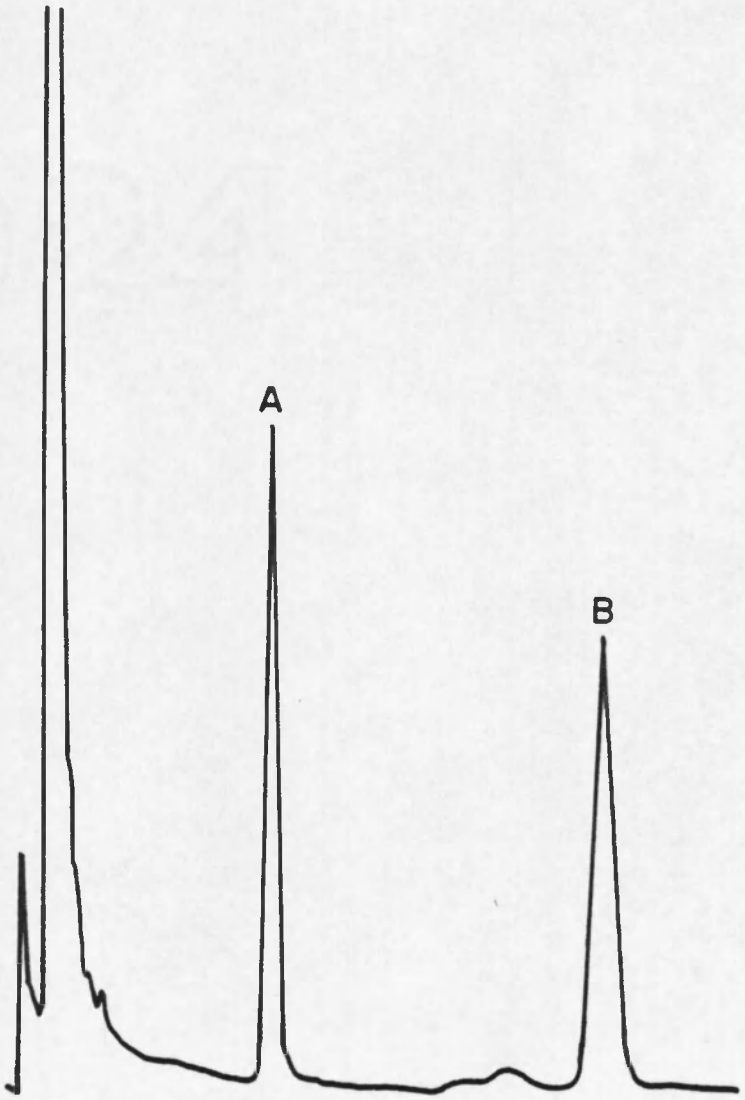


Figure 8. Gas chromatogram of a plasma sample containing mepivacaine, processed by Method B. -- Gas chromatogram of mepivacaine and internal standard (chlorpheniramine maleate) extracted from plasma by Method B. Key: A, chlorpheniramine maleate; B, mepivacaine.

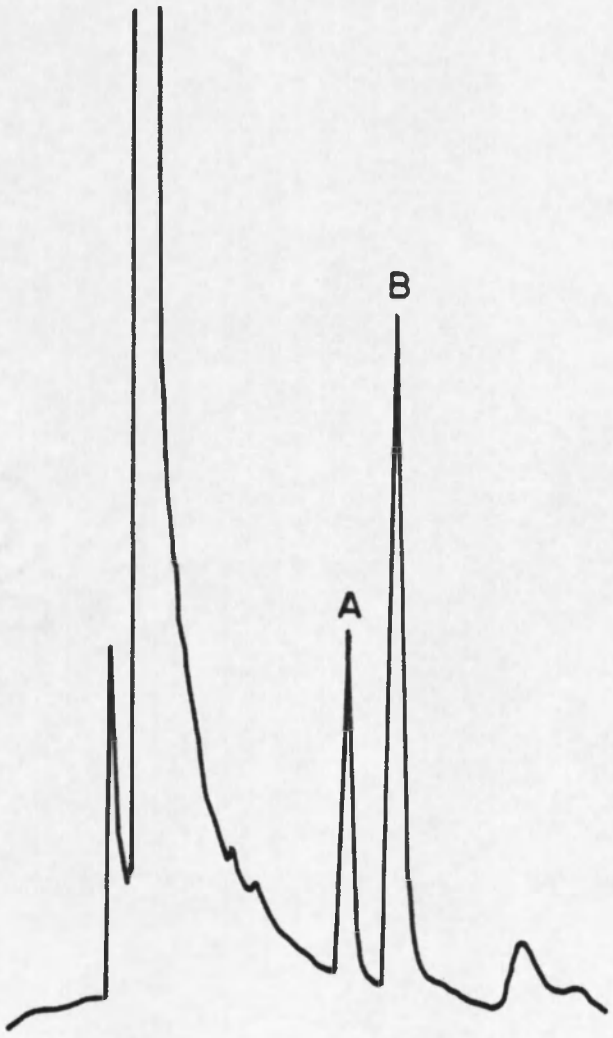


Figure 9. Gas chromatogram of a plasma sample containing lidocaine, processed by Method B. -- Gas chromatogram of lidocaine and internal standard (chlorpheniramine maleate) extracted from plasma by Method B. Key: A, lidocaine; B, chlorpheniramins maleate.

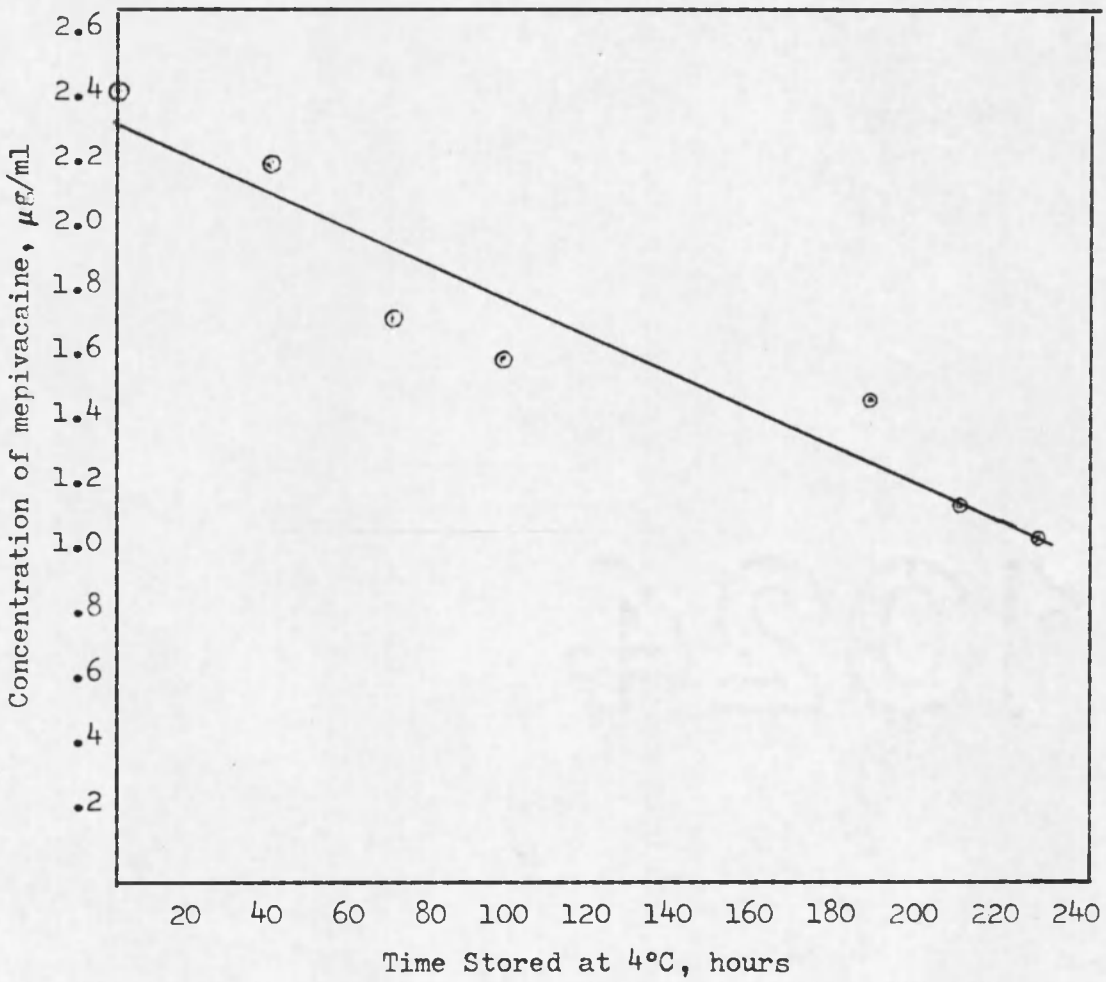


Figure 10. Decomposition of mepivacaine in whole blood.

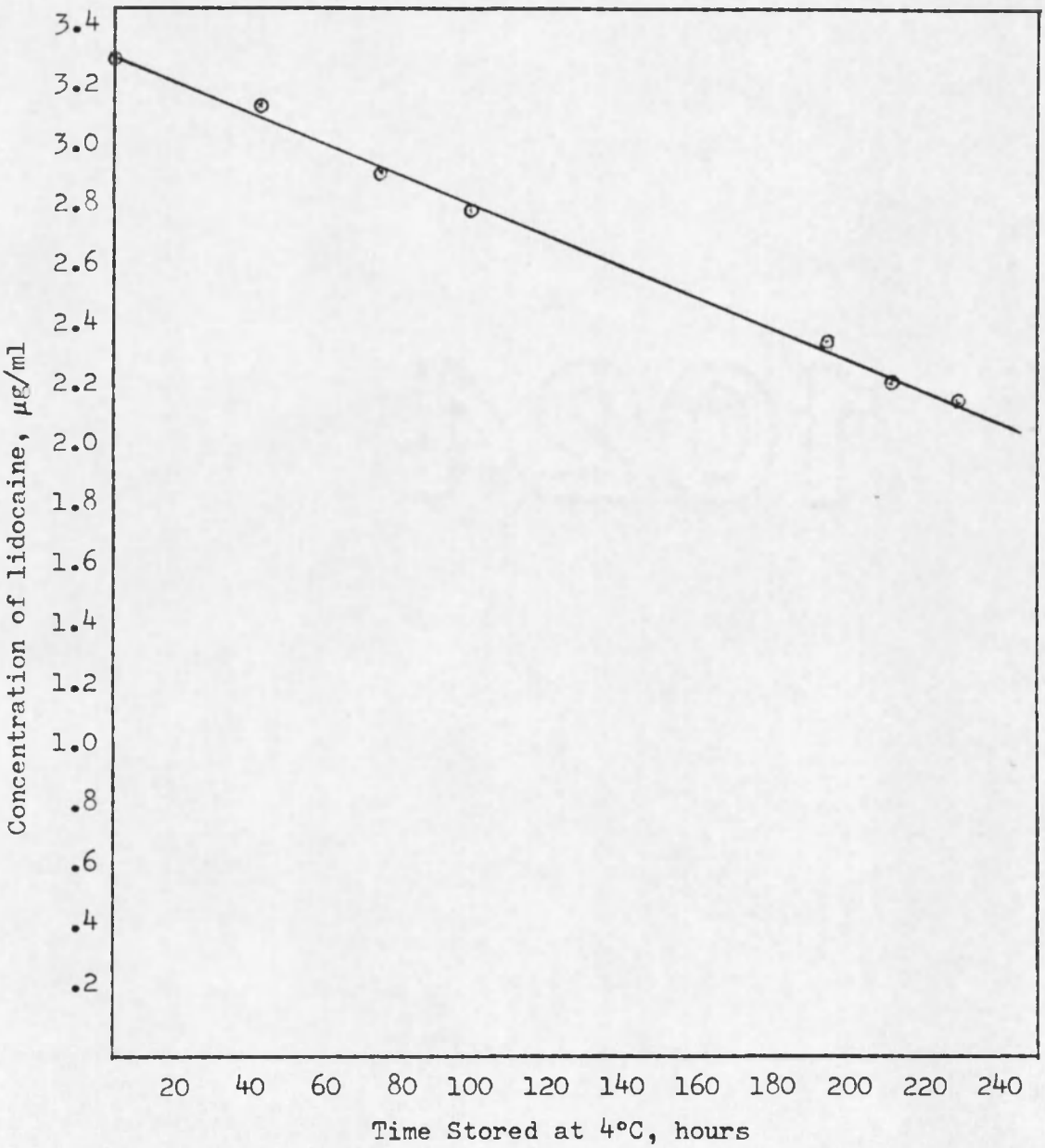


Figure 11. Decomposition of lidocaine in refrigerated whole blood.

Arizona Health Sciences Center Study

Cord blood samples were obtained from the Arizona Health Sciences Center Blood Bank. Over the period of 1.5 years, 192 randomly selected samples from this institution were analyzed for local anesthetic levels. Detectable levels of local anesthetics were found in 58 of the 100 samples that yielded reportable results. The mean cord blood concentration of mepivacaine was 1.42 μg/ml, with a range of 0.-9.0 μg/ml. The mean concentration of lidocaine was 1.11 μg/ml (range, 0.24-2.98 μg/ml).

Figure 12 demonstrates the distribution of mepivacaine and lidocaine levels in the samples containing detectable levels of the drugs. The highest occurrence of mepivacaine levels was in the 0.2 to 0.4 range, and in the 0.8-1.0 μg/ml range. For lidocaine, the highest incidence of detectable levels was in the 1.0-1.2 μg/ml range.

The medical chart of each patient was reviewed, and pertinent clinical data were tabulated with the level of local anesthetic detected in each blood sample. The data are presented in Appendix A.

Since the analyses of the cord blood samples were performed independently of the chart reviews, the chart data represented an opportunity to evaluate the reliability of the analytical methodology. Method A was used to process 56 samples. Mepivacaine was administered to 37 of these patients, and the drug was detected in the cord blood of 25 infants. The remaining 44 samples were processed by Method B, and 35 of these patients received mepivacaine or lidocaine. The agents were detected in the cord blood of 28 of the infants. The success at which the methods detected administered local anesthetics was compared

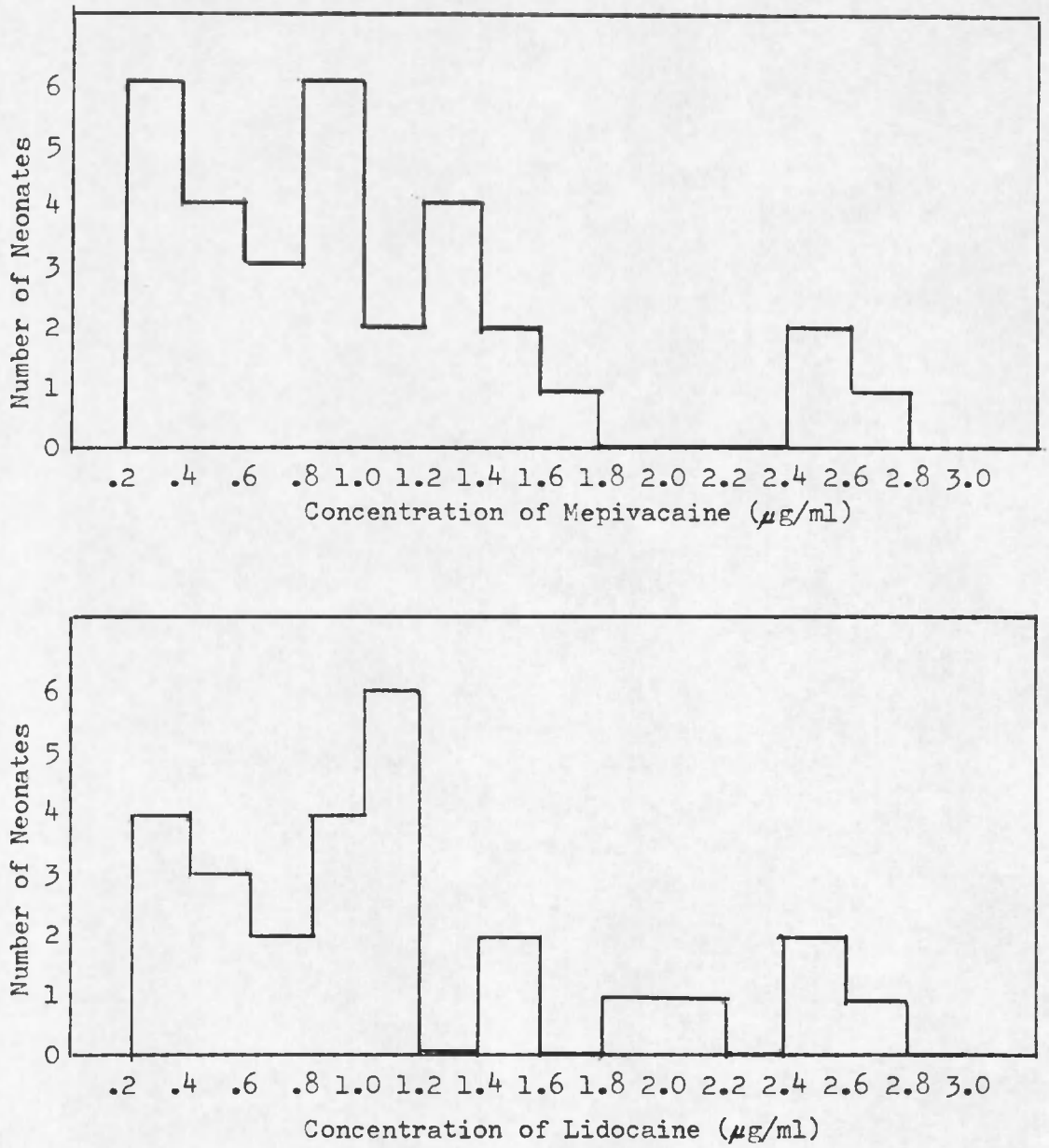


Figure 12. Distribution of detectable levels of local anesthetics: Arizona Health Sciences Center Study.

by a Chi-square calculation. These results are presented in Table 3. The two methods were not significantly different.

Cases were encountered in which the data were "falsely positive," or in which a cord blood sample contained mepivacaine or lidocaine, but the patient's chart did not record any administration of the drug. Method B yielded one falsely positive result and Method A yielded four.

It was of interest to determine whether there were any correlations between the routes of administration of mepivacaine and lidocaine, the resulting cord blood concentrations, and the condition of the neonates at birth as indicated by the Apgar Score. The clinical and analytical data were divided into separate groups according to the route of administration of each drug. Cases of premature delivery were not included in these groupings. The sample mean ($\overline{X}$), the standard deviation (S), and the standard deviation of the sample mean ($S_{\overline{X}}$) of the analytical data and the Apgar Score were calculated. These results are presented for mepivacaine and lidocaine in Tables 4 and 5, respectively, and show that higher levels of mepivacaine and lidocaine and lower Apgar Scores of the neonates appear to be associated with paracervical or pudendal anesthesis. Interpretation of these data was difficult because of the high standard deviation within a given route of administration.

For patients receiving lidocaine, the highest mean cord blood level of the drug, 1.50 μg/ml, was found in the pudendal anesthesia group. The two tailed student's t-test indicated that the mean concentration of lidocaine in this group was significantly higher than the

Table 3. Chi-square comparison of Method A and Method B: success of detecting local anesthetics in dosed patients.

Analytical Methodology	Anesthetics Detected	Anesthetics Not Detected	Patients Dosed (Total)
Method A	25	12	37
Method B	28	7	35
Total	53	19	72

$X^2 = 1.431$
$P \leq 0.24$

Table 4. Correlations between route of administration of lidocaine, analytical data and Apgar Scores.

Route	Number of Cases	Anesthetic Levels mean	S	$S_{\bar{X}}$	Apgar Scores mean	S	$S_{\bar{X}}$
Paracervical	1	2.50	*	*	7.0	*	*
Pudendal	10	1.50	0.88	0.28	6.7	2.4	0.8
Local	7	0.42	0.42	0.16	8.4	1.1	0.5
Pudendal plus local	7	0.72	0.39	0.15	7.6	1.3	0.5

*With only 1 case, calculation of S and $S_{\bar{X}}$ was not possible.

Table 5. Correlations between route of administration of mepivacaine, analytical data and Apgar Score.

Route	Number of Cases	Anesthetic Levels mean	S	S_X	Apgar Scores mean	S	S_X
Paracervical	5	1.56	1.93	0.86	7.8	1.3	0.6
Pudendal	20	1.05	1.98	0.44	8.1	1.7	0.4
Local	3	0.43	0.75	0.43	7.0	2.0	1.1
Paracervical plus Pudendal	11	0.56	0.48	0.14	8.3	0.8	0.2
Pudendal plus Local	1	1.55	*	*	9.0	*	*
Paracervical plus Local	2	0.7	0.98	0.96	9.0	0.0	0.0
Epidural	1	1.7	*	*	9.0	*	*

*With only 1 case, calculation of S and S_X was not possible.

mean level in the other groups ($P < 0.04$). These results are presented in Table 6.

For patients receiving mepivacaine, the analytical data seem to indicate that paracervical block anesthesia results in higher neonatal cord block levels. However, the differences between the groups were not statistically significant ($P < 0.80$). There were no significant differences in Apgar Scores between the groups ($P < 0.30$). These comparisons are listed in Table 7.

Six amnionic fluid samples were examined for the presence of local anesthetics. After the amnionic cells had been collected from these samples, the remaining fluid was frozen. These frozen samples were obtained from the Arizona Health Sciences Center. All the samples were analyzed on the same day. Lidocaine was detected in four of these samples. The concentrations ranged from 0.1 μg/ml to 0.7 μg/ml. The analytical data are summarized in Table 8.

Samples of blood, urine and gastric aspirates obtained from an infant displaying obvious signs of mepivacaine toxicity were assayed for mepivacaine. Levels of mepivacaine were detected in all of the samples. The concentration in the gastric aspirates, at 3.8 μg/ml, and the 24 hour pooled urine, at 3.0 μg/ml, were higher than the level of the drug in the infant's blood (0.4 μg/ml). Blood and urine specimens were obtained from a second infant displaying mepivacaine toxicity. The concentrations of mepivacaine in the blood and urine were 0.4 and 2.1 μg/ml, respectively. The data are listed in Table 9.

Table 6. Significance of correlations between routes of administration of lidocaine, analytical data and Apgar Scores.

Route A	Route B	Mean Levels of Lidocaine x_A	x_B	Probability*	Mean Apgar Scores x_A	x_B	Probability*
Pudendal	Local	1.50	0.42	<0.09	6.7	8.4	<0.27
Pudendal	Pudendal plus Local	1.50	0.72	<0.045	6.7	7.6	<0.39
Pudendal plus Local	Local	0.72	0.42	<0.22	7.6	8.4	<0.24

*Probability $\leq$ 0.05 is statistically significant.

Table 7. Significance of correlations between routes of administration of mepivacaine, analytical data and Apgar Scores.

Route A	Route B	Mean Levels of Mepivacaine		Probability*	Mean Apgar Scores x_A	x_B	Probability*
Paracervical	Pudendal	1.56	1.05	<0.68	7.8	8.1	<0.77
Paracervical	Local	1.56	0.43	<0.38	7.8	7.0	<0.59
Paracervical	Paracervical plus Pudendal	1.56	0.56	<0.12	7.8	8.3	<0.48
Paracervical	Paracervical plus Local	1.56	0.70	<0.59	7.8	9.0	<0.45
Local	Pudendal	0.43	1.05	<0.60	7.0	8.1	<0.32
Paracervical plus Pudendal	Pudendal	0.56	1.05	<0.43	8.3	8.1	<0.72
Paracervical plus Local	Pudendal	0.70	1.05	<0.77	9.0	8.1	<0.09
Paracervical plus Local	Paracervical plus Pudendal	0.70	0.56	<0.75	9.0	8.3	<0.25
Paracervical plus Local	Local	0.70	0.43	<0.75	9.0	7.0	<0.27
Paracervical plus Pudendal	Local	0.56	0.43	<0.72	8.3	7.0	<0.09

*Probability $\leq$ 0.05 is statistically significant.

Table 8. Results of analyses of amnionic fluid samples.

Case Number	Anesthetic Detected	Level (μg/ml)
A1	lidocaine	0.38
A2	lidocaine	0.67
A3	lidocaine	0.70
A4	lidocaine	0.10
A5	none detected	-
A6	none detected	-

Table 9. Results of analyses of samples from mepivacaine toxicity cases.

Case Number	Sample Type	Level (μg/ml)
M1	cord blood	0.4
	urine	2.1
M2	cord blood	0.4
	urine (24 hrs)	3.0
	gastric aspirates	3.8

Tucson Medical Center Study

A total of 103 cord blood samples from the Tucson Medical Center Blood Bank were analyzed for the presence of mepivacaine and lidocaine over a four month period. All the samples were analyzed by Method B. Only the analytical data were evaluated, because the charts were not available for review. Local anesthetics were detected in 59% of the 100 samples that were successfully analyzed. The mean concentration of mepivacaine found was 1.23 μg/ml (range, 0.10-3.08 μg/ml). The mean level of lidocaine detected was 0.76 μg/ml (range, 0.34-2.04 μg/ml). The analytical data are tabulated in Appendix B.

Figure 13 demonstrates the distribution of mepivacaine and lidocaine levels in the samples containing detectable levels of the drugs. The greatest number of mepivacaine levels were in the 1.0-1.4 μg/ml range. For lidocaine, the highest incidence of detectable levels were in the 0.4-0.6 μg/ml range.

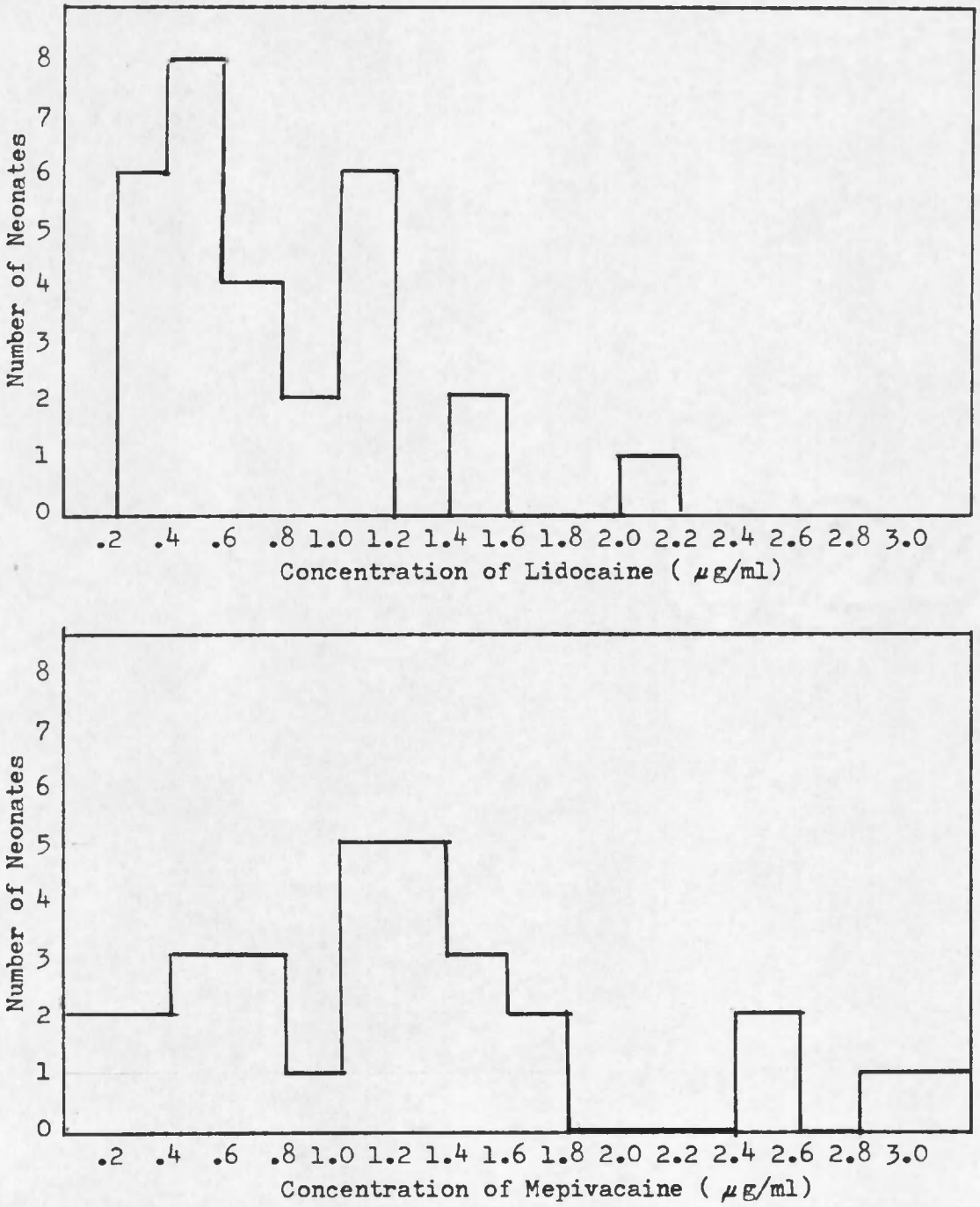


Figure 13. Distribution of detectable levels of local anesthetics: Tucson Medical Center Study.

DISCUSSION

Analytical Methodology

The chromatographic conditions described by Thomas and Meffin (1972) provided adequate separation of the mepivacaine, lidocaine, and bupivacaine peaks. The extraction procedures were developed for the cord blood samples. Both extraction procedures were modifications of the procedure recommended by Thomas and Meffin.

In Method A the procedure outlined by Thomas and Meffin was followed with a single modification. Carbon disulfide was used as the injection solvent because it was not possible to chromatograph ether solutions of the plasma extracts as Thomas and Meffin recommended (P. Meffin personal communication 1974). Mepivacaine levels in almost all of the samples were low (0.5-2.0 μg/ml). Therefore, it was necessary to inject at least two microliters in order to quantitate the mepivacaine peak. Since ether itself had a high FID response, a two microliter injection resulted in an unacceptably large solvent peak. Use of carbon disulfide alleviated this problem.

Although the data on Tables 2 and 3 indicated that analytical procedures A and B provided comparable results, it became apparent that Method A did not afford an adequate cleanup procedure for cord blood samples. From a total of 148 samples that were processed by Method A, reportable results were obtained for only 56 samples. The problems that were encountered may have been due to the fact that

most of the cord blood samples had undergone hemolysis by the time they were released by the blood bank. Ideally, the serum should have been recovered from these samples and frozen as soon as possible after the time of birth. Under better experimental conditions, the extraction procedure described by Thomas and Meffin may have provided a sufficient cleanup procedure.

The use of ether as the final extraction solvent was the cause of most of the problems that were encountered with Method A. Lipids and other contaminants in the cord blood samples were extracted along with the compounds of interest and these peaks interfered with the bupivacaine peak. Often, extraneous peaks extracted by the ether eluted after the mepivacaine and bupivacaine peaks, prolonging analysis time. A total of 21 of the processed samples were contaminated to the point that solids were visible in the final injection mixture. These samples were not injected. The apparatus and reagents were additional sources of contamination. Contaminants were introduced from the glassware and the base solution used in the procedure. The final evaporation step proved to be a problem as contaminants were introduced by the nitrogen gas cylinders. Once the evaporation step was completed, it was necessary to reconstitute and inject the samples almost immediately. Otherwise, extraneous peaks appeared in the sample chromatogram. Due to the extreme volatility of carbon disulfide, the final injection mixture evaporated.

The extraction procedure was modified to avoid the problems encountered in the original method. Chlorpheniramine maleate was used as the internal standard, because chromatograms of drug free cord blood

samples showed no interfering peaks at its retention time. The local anesthetics were extracted into carbon disulfide from the aqueous alkaline phase directly, thus avoiding the final evaporation step. Because carbon disulfide extracted fewer lipids from the hemolyzed cord blood than diethyl ether, direct extraction of the anesthetics into carbon disulfide resulted in cleaner chromatograms. The improved quality of the chromatograms allowed the simultaneous analysis of mepivacaine and lidocaine because it was then possible to resolve and quantitate the lidocaine peak. Since the carbon disulfide injection solution remained beneath the aqueous layer, the problem of solvent evaporation was eliminated. Closer attention was paid to glassware and solvent purity, thus improving the chromatograms. When Method B was used, reportable results were obtained for 46 samples from the Arizona Health Sciences Center and 100 samples from the Tucson Medical Center. Only 3 samples were discarded due to assay problems.

The procedure for analyzing lidocaine was tedious. Adsorptive losses made quantitation of this compound difficult. It was assumed that this was due to a chromatography problem, because the calibration plot did not intercept the origin, and similar problems were encountered when lidocaine standards were injected. Injections of small amounts of 5% dichlorodimethyl silane in toluene along with frequent injections of lidocaine standards during sample analyses minimized but did not eliminate this problem. The adsorptive problems might be avoided by choosing more suitable chromatographic conditions. A less polar stationary phase, such as OV-17, could improve the situation.

Stability Study

The stability study was an attempt to demonstrate the behavior of mepivacaine and lidocaine in whole blood samples under storage conditions similar to those in the blood bank. The results of the stability study indicated that the analytical data reported for the patients may have been systematically low. Both mepivacaine and lidocaine suffered decomposition in refrigerated whole blood samples. The cord blood samples released by the blood bank had been refrigerated for at least 7 days. It was obvious that the blood levels of local anesthetics at birth were higher than the measured levels. If the analytical data in Appendices A and B were adjusted to reflect the decomposition of mepivacaine and lidocaine seen in the stability study, the levels of the two drugs would be, respectively, 2.4 times and 1.5 times the reported amounts.

The data from the stability study should be interpreted cautiously, however. The decomposition of mepivacaine seemed to be inordinately high. Moreover, the results from three of three of the seven mepivacaine stability samples did not conform to the proposed degradation patterns. The stability pattern of the lidocaine samples appeared to be satisfactory.

The analytical method was not capable of detecting the decomposition products of mepivacaine or lidocaine. In both the mepivacaine and the lidocaine stability studies, peaks due to possible degradation products were not observed in the sample chromatograms. It does not seem likely that the decomposition products would be separated from the intact anesthetic molecules during the extraction procedure,

because only acidic or non-ionizable compounds would be separated during the extraction.

This study was performed using 21 ml of blood from one adult subject. Since degradation patterns could vary between subjects, and between adult and neonatal blood, actual samples from patients may not prove that both drugs undergo decomposition in refrigerated whole blood samples. Further conclusions should not be drawn without additional data.

Arizona Health Sciences Center Study

Analytical Determinations

Detectable levels of mepivacaine (> 0.1 $\mu g/ml$) or lidocaine (> 0.15 $\mu g/ml$) were found in 58% of the cases at The Arizona Health Sciences Center. The actual incidence of detectable levels in this study may even be higher. Because assay problems were encountered with Method A, 71 samples containing mepivacaine did not yield reportable results. Quantitation of these samples was impossible, because extraneous peaks interfered with the peaks of interest. Samples which did not contain mepivacaine did not present quantitation problems. A higher proportion of these samples yielded reportable results.

The comparison between Method A and Method B on Table 4 did not show that Method B was superior to Method A at detecting a local anesthetic in the cord blood of a patient whose chart recorded its administration. If the sample populations were larger, it might be possible to demonstrate significant differences between the two methods. However, comparison of the success of obtaining reportable

results from processed cord blood samples indicated that Method B was superior to Method A ($P < 0.01$). The chi square analysis of this comparison is presented in Table 10.

That Method A yielded more falsely positive results than Method B would seem to indicate that Method B was more reliable. These data should be interpreted cautiously, however. Although falsely positive results might be due to assay errors, they could also be due to recording errors on the patients' charts. Moreover, the incidence of falsely positive results in Method A and Method B ($P = 0.28$) was not significantly different.

The mean concentration of mepivacaine found in the 33 samples containing the drug was 1.42 μg/ml. Most of the blood samples contained levels of mepivacaine below the mean concentration. The distribution of mepivacaine concentrations, as Figure 9 illustrates, was highest in the 0.2-0.4 μg/ml and the 0.8-1.0 μg/ml ranges. It should be noted that there were 2 samples with unusually high concentrations (5 μg/ml and 9 μg/ml). If these levels were removed from the data, the mean concentration of mepivacaine would be 0.99 μg/ml. The detect levels of mepivacaine are distributed more normally around a mean of 0.99 μg/ml.

The mean concentration of lidocaine detected in the 26 samples containing this agent was 1.11 μg/ml. This mean level compared favorably with the distribution of lidocaine levels found in the samples. The distribution of the levels of lidocaine, like mepivacaine, was weighted toward the lower concentrations.

Table 10. Chi-square comparison of Method A and Method B: success of obtaining reportable results from processed samples.

Analytical Methodology	Successful Analyses	Unsuccessful Analyses	Total Analyses
Method A	56	92	148
Method B	144	2	144
Total	200	94	294

$\chi^2 = 169.8$
$P \leq 0.01$

It had been postulated that the fetal thresholds of toxicity of mepivacaine and lidocaine were approximately half the values of the maternal thresholds of toxicity. For both agents, the fetal toxic threshold has been postulated to be approximately half the level of the maternal toxic threshold (Shnider and Way 1968b; Morishima et al. 1966). The mean levels of mepivacaine and lidocaine detected in the cord blood samples seemed to be below the drugs' fetal toxic thresholds. However, two cord blood samples contained mepivacaine levels in excess of 5 μg/ml. Moreover, the results of the stability studies indicated that the cord blood concentrations of the drugs at birth have been higher than the concentrations at the time of analysis. It would seem that the reported values for the fetal toxic threshold should be adjusted to allow for the decomposition of the agents observed in the stability study. If a blood sample containing a toxic level (3 μg/ml) of mepivacaine were stored in the Arizona Health Services Center Blood Bank, the concentration would be 1.41 μg/ml after 10 days. If a sample containing a toxic concentration of lidocaine (5.3 μg/ml) were stored under these conditions, the concentration would be 1.95 μg/ml after 10 days. The analytical data showed that the cord blood samples of six infants contained mepivacaine concentrations in excess of 1.41 μg/ml. Levels in excess of 1.95 μg/ml of lidocaine were detected in 5 samples.

Clinical Data

Comparisons of neonatal blood levels and Apgar Scores following administration of lidocaine by various routes of administration have not been reported in the literature. The data on Table 7

indicated that neonatal blood levels of lidocaine following pudendal anesthesia were significantly higher than levels following local anesthesia or a combination of local and pudendal anesthesia. The multiple injections of the agent (pudendal plus local) resulted in lower blood levels than a single injection was unexpected. Interpretation of these results was complicated by the fact that the patients' chart data were not complete. None of the charts recorded the dose of lidocaine given and 50% of the 24 charts did not record the time of administration.

There were no statistically significant correlations between the routes of administrations of mepivacaine and the resulting neonatal cord blood levels. Although the neonatal blood levels resulting from paracervical block anesthesia appeared to be higher than those resulting from a combination of paracervical and pudendal anesthesia, the differences were not statistically significant ($P < 0.10$). It should be noted that the time intervals between administration of the drug and delivery were shorter in the paracervical block anesthesia group. This might explain the apparently higher blood levels following paracervical block anesthesia alone. It was not possible to relate the neonatal blood levels to the administered dose of mepivacaine in these two groups, because 13 of the 15 charts did not record the dose given.

The condition of the neonates as indicated by the Apgar Scores were not significantly different in any of the groups compared in Tables 5 and 6. Although there were cases of infants whose cord blood levels of anesthetics were high and whose Apgar Scores were depressed, the level of significance exceeded $P < 0.20$ in all the groups.

Statistical interpretation of the clinical data was complicated by the fact that there were numerous variables in this study. The reliability of the Apgar Score was questionable: this evaluation procedure can be subject to operator to operator bias (Greenhill and Briedman 1974, pp. 247). In addition, experimental conditions were not controlled. Intravenous injections of meperidine were given to 53% of the patients in the Arizona Health Services Center Study. Meperidine, a synthetic narcotic analgesic, readily crosses the placental space and can have a depressant effect on the neonate (Evans, Hogg and Rosen 1976). A total of 21% of the deliveries were complicated by premature delivery, maternal health problems or maternal drug abuse. The condition of the neonates as measured by the Apgar Scores was dependent on all of these parameters in addition to the presence of local anesthetics.

Amniocentesis Samples

Often, local anesthesia is used during the amniocentesis procedure. That detectable levels of lidocaine were found in four of the six samples analyzed is a cause for concern. The patients' charts were not available. If patient information had been available, it may have been possible to draw conclusions about the presence of lidocaine in amnionic fluid following amniocentesis. The mature human fetus swallows approximately 450 ml of amnionic fluid per day. For immature fetuses, volumes of amnionic fluid swallowed per day range from as little as 7 ml, by a fetus of approximately 16 weeks gestational age to 120 ml, by a fetus of about 28 weeks of gestational age (Pritchard 1966). The consequences of exposing the fetus to low levels of local

anesthetics are not known. It is possible that the local anesthetic is cleared quickly. It is known that the amnionic fluid is completely replaced on the average of once every 2.9 hours (Greenhill and Briedman 1974, pp. 186). Most authors recommend that exposure of the fetus to any drugs during pregnancy be minimized. Greenhill and Briedman contend that the use of local anesthetic agents for amniocentesis is optional, and tends not to be needed. It would seem to be advantageous to minimize the use of local anesthetics in this procedure.

Toxicity Cases

The data in Tables 8 and 9 indicated that the extraction procedure afforded a sufficient cleanup procedure for gastric aspirates and urine. The high levels of mepivacaine in the gastric aspirates were due to fetal swallowing of the amnionic fluid, fetal micturition and ion trapping due to the pH of the digestive system (Brown et al. 1977). The concentrations of mepivacaine in both infants' urine were higher than the concentrations of mepivacaine in the blood samples. This supported evidence in the literature that the drug is cleared quickly from the human neonate (Meffin, Long and Thomas 1972).

Tucson Medical Center Study

Analytical Determinations

Many of the deliveries at The Arizona Health Services Center were high risk pregnencies. It must be recognized that the clinical data obtained from this institution did not reflect the consequences of local anesthetics in normal obstetric practice. One hundred cases

from Tucson Medical Center were studied because it was felt that Tucson Medical Center, a community hospital, would be a more reliable indication of the use of local anesthetics in normal obstetric practice.

One method, Method B, was used to obtain the analytical data for these samples. Since problems were not encountered with the analytical method, the analytical data from Tucson Medical Center were more homogeneous than the Arizona Health Sercices Center data.

The mean cord blood concentrations of mepivacaine and lidocaine in the samples from Tucson Medical Center were below the fetal toxic thresholds of the two drugs. There was one sample in which the concentration of mepivacaine was slightly above the fetal toxic threshold (3.08 μg/ml). However, the literature values for the fetal toxic thresholds of mepivacaine and lidocaine should again be adjusted to reflect the decomposition that the agents underwent in the stability study. The concentration of mepivacaine in 10 cord blood samples exceeded 1.41 μg/ml, and the concentration of lidocaine in one sample exceeded 1.95 μg/ml. The justification for lowering the reported values for the toxic thresholds of mepivacaine and lidocaine was discussed previously.

It was not possible to obtain the patients' charts for the Tucson Medical Center study. This was unfortunate because the analytical data for mepivacaine appeared to be more homogeneous than the data from the Arizona Health Services Center. The samples were analyzed over a short times, so the analytical data from Tucson Medical Center were subject to fewer variables. It is likely that

more conclusions might have been drawn concerning the analytical data and the route of administration of the anesthetics.

CONCLUSION

Two methods capable of detecting μg amounts of mepivacaine in neonatal cord blood were developed. Chromatographic conditions in both methods were identical. One method, Method B, was capable of quantitating mepivacaine and lidocaine simultaneously. This method proved to be better suited for analyzing cord blood samples. The extraction procedures were capable of detecting μg amounts of the agents in biological other media (urine, gastric aspirates, amnionic fluid).

There was a significant incidence of detectable blood levels of mepivacaine and lidocaine in a sampling of 100 patients from each of two hospitals. The infants were exposed to higher levels of the agents than the levels detected, because mepivacaine and lidocaine had decomposed under storage conditions in the hospital blood banks. Allowing for the decomposition of the samples prior to analyses, it would seem that a total of 13 neonates from the Arizona Health Sciences Center and 12 neonates from Tucson Medical Center had been exposed to levels of local anesthetics that exceeded the fetal threshold of toxicity.

In the Arizona Health Sciences Center study, the routes of administration of lidocaine showed statistically significant correlations ϕ to the neonatal cord blood levels of the agent. However, that neonatal cord blood levels of lidocaine following pudendal

anesthesia were significantly higher than the levels following a combination of pudendal anesthesia and local anesthesia was unexpected. Neonatal cord blood levels following regional anesthesia using mepivacaine were not significantly correlated to the route of administration of the agent. The condition of the neonate as measured by the Apgar Score was not related to the route of administration of the local anesthetic or to the cord blood concentration of the agent at birth.

Lidocaine was detected in 4 of the 6 amnionic fluid samples analyzed. These samples were collected for diagnostic amniocentesis.

Samples from Tucson Medical Center were analyzed because it was felt that the cases encountered at the Arizona Health Sciences Center were not indicative of normal obstetric practice. The clinical data were not evaluated because the patients' charts were not available.

APPENDIX A

ANALYTICAL AND CLINICAL DATA FROM ARIZONA HEALTH SCIENCES CENTER STUDY

In the Level of Anesthetic column, the following symbols are used to differentiate between mepivacaine and lidocaine:

L = lidocaine

M = mepivacaine

Table A1. Summary of analytical and clinical data.

Case Number	Maternal Analgesia			Local Anesthesia			Clinical Data		
	Medication	Administra. Route	Time	Anesthetic	Route of Administration	Time Before Delivery	Complications	Apgar Score	Level of Anesthetic (μg/ml)
1	none	-	-	Lidocaine	Pudendal	-	Uncomplicated	9-9	0.24 L
2	Sparine Demerol	IV IV	2h 25m 2h 25m	Mepivacaine	Paracervical	1h 35m	Late deceler-ation	10-10	0.48 M
3	Sparine Demerol	IV IV	1h 35m 1h 35m	Lidocaine	Local plus Pudendal	-	jaundiced	9-9	0.40 L
4	none	-	-	Lidocaine	Local	-	Premature (27 wks)	2-3	1.53 L
5	Demerol	IV	1h 30m	Lidocaine	Pudendal	30m	jaundiced	6-7	2.02 L
6	Sparine	-	-	Bupivacaine Lidocaine	Paracervical Pudendal	1h 7m 12m	Thrombo-phlebitis	6-7	0.00 M 1.16 L
7	Demerol Sparine	IV IV	1h 19m 1h 19m	Lidocaine	Pudendal	24m	meconium stain	2-10	1.09 L
8	none	-	-	Lidocaine	Local	11m	Uncomplicated	9-10	1.15 L
9	Sparine	IV	1h 22m	Lidocaine	Pudendal	-	Uncomplicated	9-10	0.44 L
10	Morphine	IM	13h 33m	Lidocaine	Local	12m	jaundiced	8-10	0.31 L
11	Demerol Demerol Demerol	IV	3h 10m 1h 55m 40m	Mepivacaine Lidocaine	Paracervical Pudendal	4h 15m	Resustitation necessary	5-7	1.0 M 1.12 L
12	none	-	-	Lidocaine	Local plus Pudendal	-	jaundiced	7-9	0.97 L
13	none	-	-	Lidocaine	Local plus Pudendal	-	jaundiced	7-9	0.97 L

Table A1--Continued. Summary of analytical and clinical data.

Case Number	Maternal Analgesia: Medication	Administra. Route	Administra. Time	Local Anesthesia: Anesthetic	Route of Administration	Time Before Delivery	Clinical Data: Complications	Apgar Score	Level of Anesthetic (μg/ml)
14	Demerol Sparine	IV IV	3h 3h	Lidocaine	Local plus Pudendal	-	Uncomplicated	8-8	0.97 L
15	Demerol Sparine	IV IV	5h 5h	Lidocaine	Local	10m	Flarine	9-10	0.35 L
16	Demerol Sparine	IV IV	6h 17m 6h 17m	Lidocaine	Local	-	Uncomplicated	9-10	0.35 L
17	none	-	-	Lidocaine	Local plus Pudendal	14m	jittery	8-9	0.86 L
18	Demerol Sparine Demerol Sparine	IV IV IV IV	6h 40m 6h 30m 3h 23m 3h 23m	Lidocaine	Pudendal	-	Uncomplicated	8-9	1.50 L
19	Demerol Sparine	IV IV	1h 2m 1h 2m	Bupivacaine Lidocaine	Paracervical Local	37m -	Uncomplicated	9-10	0.00 M 0.82 L
20	none	-	-	Lidocaine	Local	9m	Nuccal cord	6-8	0.00 L
21	General	-	-	-	-	-	Premature	6-9	-
22	General	-	-	-	-	-	Congenical abnormalities	1-1	-
23	none	-	-	Mepivacaine	Pudendal	-	Heart murmur	7-9	0.0 M
24	General	-	-	-	-	-	Maternal diabetes	9-9	-
25	Demerol Sparine	IV IV	2h	none	-	-	Uncomplicated	7-9	-

Table A1--Continued. Summary of analytical and clinical data.

Case Number	Maternal Analgesia			Local Anesthesia			Clinical Data		
	Medication	Administra. Route	Time	Anesthetic	Route of Administration	Time Before Delivery	Complications	Apgar Score	Level of Anesthetic (μg/ml)
26	none	-	-	?	Local	-	Anemia, jaundiced	9-10	0.00 L 0.00 M
27	General	-	-	-	-	-	Premature Maternal renal failure	7-9	-
28	Sparine	IV	1h 46m	Bupivacaine	Paracervical	1h 23m	Premature	7-7	0.00 M
29	none	-	-	Lidocaine	Pudendal	52m	Uncomplicated	9-9	2.54 L
30	Demerol Sparine	IV IV	50m 50m	Mepivacaine	Local	5m	Sleepy	7-8	0.00 M
31	none	-	-	Mepivacaine Mepivacaine	Paracervical Pudendal	2h 44m	Uncomplicated	9-10	0.00 M
32	Demerol Sparine	IV IV	1h 23m 1h 23m	Mepivacaine	Pudendal	-	Uncomplicated	8-9	0.00 M
33	General	-	-	-	-	-	Maternal diabetes	3-7	-
34	none	-	-	-	-	-	jaundiced	8-9	-
35	none	-	-	-	-	-	jaundiced	7-8	-
36	Demerol Sparine	IV IV	1h 33m 1h 8m	none	-	-	Uncomplicated	7-8	0.00 M
37	Demerol Sparine	IV IV	20m 20m	none	-	-	Sepsis	5-8	-

Table A1--Continued. Summary of analytical and clinical data.

Case Number	Maternal Analgesia: Medication	Administra. Route	Administra. Time	Local Anesthesia: Anesthetic	Route of Administration	Time Before Delivery	Clinical Data: Complications	Apgar Score	Level of Anesthetic (μg/ml)
38	Demerol	IV	33m						
	Sparine	IV	33m	Lidocaine	Local	6m	Premature	6-8	0.00 L
39	$MgSO_4$	IV	3h 28m						
	Demerol	IV	2h 30m	Lidocaine	Pudendal plus Local	10m	Uncomplicated	8-10	0.00 M
	Sparine	IV	2h 30m						0.00 L
40	Morphine	IM	7h 40m						
	Nembutal	IM	7h 40m						
	Demerol	IV	1h 45m	Lidocaine	Pudendal plus Local	10m	Meconium stain	5-6	0.00
	Sparine	IV	2h 25m						
41	General	-	-	none	-	-	Sunset eyes	8-9	0.00
42	General	-	-	none	-	-	Premature	5-6	-
43	none	-	-	none	-	-	Uncomplicated	8-9	-
44	none	-	-	Lidocaine	Pudendal	?	Premature	5-8	0.00 L
45	none	-	-	Lidocaine	Pudendal	?	Premature	9	0.00 L
46	General	-	-	none	-	-	neonatal asphyxia	1-4	-
47	none	-	-	Tetracaine	Spinal	?	Maternal diabetes	2-9	2.5 M
48	Demerol	IV	2h 23m	Mepivacaine	Paracervical	53m			0.00 M
	Demerol	IV	18m	Lidocaine	Local	?	jaundiced	9-10	0.00 L
49	none	-	-	Mepivacaine	Pudendal	?	Uncomplicated	7-9	1.10 M

Table A1--Continued. Summary of analytical and clinical data.

Case Number	Maternal Analgesia: Medication	Administra. Route	Time	Local Anesthesia: Anesthetic	Route of Administration	Time Before Delivery	Clinical Data: Complications	Apgar Score	Level of Anesthetic (μg/ml)
50	Demerol	IV	1h 42m						
	Sparine	IV	1h 42m	none	-	-	jaundiced	9-10	-
51	Nembutal	IV	9h 50m						
	Morphine	IM	9h 50m						
	Demerol	IV	3h 36m						
	Sparine	IV	3h 36m	Mepivacaine	Pudendal	?	Uncomplicated	9-10	0.89 M
52	Demerol	IV	1h 29m	Mepivacaine	Pudendal plus				
	Sparine	IV	1h 29m		Local	-	Lethargic	8-9	1.55 M
53	$MgSO_4$	IV	5h 30m	Mepivacaine	Paracervical	4h 55m			
	Demerol	IV	2h 55m	Mepivacaine	Paracervical	3h 55m			
				Mepivacaine	Pudendal		Toxemia	8-9	0.4 M
54	Demerol	IV	31m						
	Sparine	IV	31m	none	-	-	Uncomplicated	8-10	-
55	Demerol	IV	5h 4m	Mepivacaine	Paracervical	6h 4m	Tacchycardia		
	Sparine	IV	5h 4m	Mepivacaine	Paracervical	2h 19m	reduced reflex.		
				Mepivacaine	Pudendal			7-8	1.5 M
56	Demerol	IV	6h 50m						
	Sparine	IV	6h 50m						
	Demerol	IV	6h 7m	Mepivacaine	Pudendal	-	Late decelera-tion	9-10	1.17 M
57	Demerol	IV	18m	none	-	-	Premature (36 wks)	8	-
58	Demerol	IV	2h						
	Sparine	IV	2h	Mepivacaine	Pudendal	-	Post-mature	7-8	0.00 M

Table A1--Continued. Summary of analytical and clinical data.

Case Number	Maternal Analgesia: Medication	Administra. Route	Time	Local Anesthesia: Anesthetic	Route of Administration	Time Before Delivery	Clinical Data: Complications	Apgar Score	Level of Anesthetic (μg/ml)
59	none	-	-	Mepivacaine	Paracervical	46m	Cyanotic		
				Mepivacaine	Pudendal	11m	Jittery	9-9	0.00 M
60	Demerol	IV	1h 15m	Mepivacaine	Paracervical	2h			
	Sparine	IV	1h 15m	Mepivacaine	Local		Uncomplicated	9-10	0.00 M
61	Demerol						Resp. distress		
	Sparine	-	-	none	-	-	cyanosis	9	-
62	Demerol	IV	34m				Nuccal cord		
	Sparine	IV	34m	Mepivacaine	Local	3m	acrocyanosis	9-9	0.00 M
63	General	-	-	none	-	-	Premature (37 wks)	1	-
64	$MgSO_4$	IV	9h						
	Demerol	IV	2h 57m						
	Sparine	IV	2h 57m	Mepivacaine	Pudendal	7m	Hypoxia	9-10	0.00 M
65	Demerol	IV	28m	Tetracaine	Paracervical	1h 13m			
	Sparine	IV	28m	Mepivacaine	Pudendal	13m	Uncomplicated	9-9	0.00 M
66	Demerol	IV	2h 15m	Carbocaine	Paracervical	30m	Cyanotic		
	Sparine	IV	2h 15m	Carbocaine	Pudendal	7m		8-9	0.00 M
67	Demerol	IV	58m				Low extremity		
	Sparine	IV	58m	Mepivacaine	Pudendal	13m	pulse	8-9	1.30 M
68	$MgSO_4$	IV	2h 10m	Tetracaine	Spinal	30m	Gruntine sepsis	8-9	.4 M
69	Demerol	IV	6h 44m						
	Sparine	IV	6h 44m				Flaring re-		
	Demerol	IV	3h 4m	Mepivacaine	Paracervical	4h 34m	traction		
	Sparine	IV	3h 4m	Mepivacaine	Pudendal	34m	nuccal cord	9-10	.40 M

Table A1--Continued. Summary of analytical and clinical data.

Case Number	Maternal Analgesia: Medication	Administra. Route	Administra. Time	Local Anesthesia: Anesthetic	Route of Administration	Time Before Delivery	Clinical Data: Complications	Apgar Score	Level of Anesthetic (μg/ml)
70	none	-	-	Mepivacaine	Pudendal	30m	Breech	8-9	0.90 M
71	General	-	-	none	-	-	Premature (30 wks)	3-8	0.40 M
72	none	-	-	Mepivacaine	Pudendal	15m	jaundiced	9-9	0.40 M
73	Sparine	IM	8h 30m						
	Demerol	IV	2h 35m						
	Sparine	IV	2h 35m	Mepivacaine	Paracervical	4h			
	$MgSO_4$	IV	1h 30m	Mepivacaine	Pudendal	30m	Uncomplicated	8-9	0.50 M
74	none	-	-	Mepivacaine	Pudendal	11m	Maternal SLE	5-9	0.60 M
75	none	-	-	Mepivacaine	Paracervical	67m	High pitched		
				Mepivacaine	Pudendal	12m	cry	8-9	0.60 M
76	none	-	-	Mepivacaine	Pudendal	4m	jaundiced	9-10	0.60 M
77	Demerol	IV	2h 30m				hyper-bili-		
	Sparine	IV	2h 30m	Mepivacaine	Paracervical	15m	rubinemia	8-9	0.70 M
78	Demerol	IV	3h 59m	Mepivacaine	Paracervical	3h 59m	extra heart		
	Sparine	IV	3h 59m	Mepivacaine	Pudendal	29m	sound	9-10	0.80 M
79	Demerol	IV	2h 25m				tacchycardia,		
	Sparine	IV	2h 25m				meconium stain,		
	Demerol	IV	25m	Mepivacaine	Paracervical	2h	flaring		
	Sparine	IV	25m	Mepivacaine	Pudendal			7-10	1.0 M
80	none	-	-	Mepivacaine	Local	17m	lethargic; no		
							cry, hypotonia	5-5	1.3 M
81	none	-	-	Mepivacaine	Paracervical	58m			
				Mepivacaine	Local	17m	Post mature	9-9	1.40 M

Table A1--Continued. Summary of analytical and clinical data.

Case Number	Maternal Analgesia			Local Anesthesia			Clinical Data		
	Medication	Administra. Route	Time	Anesthetic	Route of Administration	Time Before Delivery	Complications	Apgar Score	Level of Anesthetic (μg/ml)
82	none	-	-	Mepivacaine	Pudendal	20m	Uncomplicated	9-9	1.40 M
83	Demerol	IV	35m						
	Sparine	IV	35m	Mepivacaine	Epidural	45m	Uncomplicated	9-10	1.70 M
84	Demerol	IV	50m	Tetracaine	Paracervical	1h 10m	Heroin addic-		
	Sparine	IV	50m	Mepivacaine	Pudendal	35m	tion	5-9	2.50 M
85	Demerol	IV	30m	Mepivacaine	Paracervical	2h 40m	Tacchycardia		
	Sparine	IV	30m	Mepivacaine	Paracervical	1h 15m	cyanotic	7-8	5.00 M
86	Demerol	IV	1h 35m				Cyanosis, Flar-		
	Sparine	IV	1h 35m	Mepivacaine	Pudendal	20m	ing, poor color	9-10	9.00 M
87	none	-	-	Mepivacaine	Pudendal	18m	Weak cry, nuccal cord, grunting	7-9	0.40 M
88	Demerol	-	-	none	-	-	Heart murmur	8	-
	Nalline								
89	none	-	-	Mepivacaine	Paracervical	48m			
				Mepivacaine	Pudendal	13m	Sleepy	9-10	1.00 M
90	Demerol	IV	3h 13m						
	Sparine	IV	3h 13m	Mepivacaine	Pudendal	18m	sl jaundiced	9-9	0.00 M
91	none	-	-	-	-	-	Cardiac arrest died 1hr	3-2	-
92	Demerol	IV	2h 44m						
	Sparine	IV	2h 44m	?	Local	9m	Sepsis, heart murmur	8-9	0.00 M

Table A1--Continued. Summary of analytical and clinical data.

Case Number	Maternal Analgesia: Medication	Administra. Route	Time	Local Anesthesia: Anesthetic	Route of Administration	Time Before Delivery	Clinical Data: Complications	Apgar Score	Level of Anesthetic (μg/ml)
93	Demerol	IV	7h 04m						
	Demerol	IV	5h 34m	Tetracaine	Spinal	-	Uncomplicated	7-8	0.00 M
94	none	-	-	Lidocaine	Pudendal	24m	Uncomplicated	9-9	1.98 L
95	none	-	-	none	-	-	Uncomplicated	9-9	-
96	none	-	-	Lidocaine	Local plus Pudendal	10m	Meconium stain	8-9	1.11 L
97	Demerol	IV	5h 56m						
	Sparine	IV	5h 56m						
	Demerol	IV	3h 09m				Acrocyanosis		
	Sparine	IV	3h 09m	Pentocaine	Spinal	34m	Nuccal cord	8-8	0.00 L
98	Demerol	IV	1h 39m				Nuccal cord		
	Sparine	IV	1h 39m	Lidocaine	Pudendal	24m	Resuscitated	3-7	2.98 L
99	Demerol	-	-	?	Local		Premature (28wks)		1.05 L
	Narcan								

APPENDIX B

ANALYTICAL DATA OF TUCSON MEDICAL CENTER CASES

Table B1. Summary of analytical data.

Patient Code	Concentration of Mepivacaine (μg/ml)	Concentration of Lidocaine (μg/ml)
T 1	-	.51
T 2	-	.67
T 3	-	.33
T 4	-	1.46
T 5	-	1.07
T 6	-	.37
T 7	-	.41
T 8	-	.45
T 9	-	.90
T10	-	.54
T11	-	1.12
T12	-	1.06
T13	-	.70
T14	-	2.05
T15	-	.37
T16	-	.61
T17	-	1.12
T18	-	.44
T19	-	.30
T20	-	.39
T21	-	.39
T22	-	.48
T23	-	1.50
T24	-	.93

Table B1--Continued. Summary of analytical data.

Patient Code	Concentration of Mepivacaine (μg/ml)	Concentration of Lidocaine (μg/ml)
T25	-	.69
T26	-	.49
T27	-	.82
T28	-	1.04
T29	-	.59
T30	.28	-
T31	1.26	-
T32	.81	-
T33	1.66	-
T34	1.19	-
T35	1.10	-
T36	1.61	-
T37	1.14	-
T38	1.22	-
T39	1.33	-
T40	0.55	-
T41	0.62	-
T42	1.02	-
T43	2.84	-
T44	0.77	-
T45	0.52	-
T46	0.17	-
T47	1.39	-
T48	0.29	-
T49	1.19	-
T50	2.21	-
T51	0.71	-
T52	1.42	-
T53	3.08	-
T54	0.42	-

Table B1--Continued. Summary of analytical data.

Patient Code	Concentration of Mepivacaine (μg/ml)	Concentration of Lidocaine (μg/ml)
T55	1.44	-
T56	2.58	-
T57	1.22	-
T58	1.54	-
T59	2.42	-
T60	0.16	-
T61	-	-
T62	-	-
T63	-	-
T64	-	-
T65	-	-
T66	-	-
T67	-	-
T68	-	-
T69	-	-
T70	-	-
T71	-	-
T72	-	-
T73	-	-
T74	-	-
T75	-	-
T76	-	-
T77	-	-
T78	-	-
T79	-	-
T80	-	-
T81	-	-
T82	-	-
T83	-	-
T84	-	-

Table B1--Continued. Summary of analytical data.

Patient Code	Concentration of Mepivacaine (μg/ml)	Concentration of Lidocaine (μg/ml)
T85	-	-
T86	-	-
T87	-	-
T88	-	-
T89	-	-
T90	-	-
T91	-	-
T92	-	-
T93	-	-
T94	-	-
T95	-	-
T96	-	-
T97	-	-
T98	-	-
T99	-	-
T100	-	-

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