

## PHARMACOLOGIC AND CLINICAL OBSERVATIONS WITH MEPIVACAINE

LT. COMDR. PAUL R. KNOX, (MC) USN, WILLIAM C. NORTH, M.D., PH.D., C. R. STEPHEN, M.D.

NUMEROUS studies in Europe have described the toxicology, pharmacologic actions and clinical use of the local anesthetic, mepivacaine, first reported in 1956, and have indicated it to be as safe and as potent as lidocaine. The two drugs are related structurally (fig. 1). However, we believed that certain other studies were indicated, primarily to determine if there were any significant differences between mepivacaine and lidocaine in regard to their "toxic" and pharmacologic properties. The following laboratory studies were performed in an effort to elucidate this problem further:

(1) Systemic toxicity in rabbits with subcutaneous administration, (2) systemic toxicity in dogs with intravenous administration, (3) nervous tissue toxicity in rabbits, (4) muscle tissue toxicity in rabbits, (5) spinal analgesia in dogs, and (6) duration of analgesia with sciatic nerve block in rabbits. In addition, a clinical evaluation of mepivacaine was made by performing a variety of regional nerve blocks in 264 patients.

### LABORATORY STUDIES

#### (1) SUBCUTANEOUS TOXICITY IN RABBITS

*Method: Group 1.* The backs of 12 rabbits, weighing 1.5 to 2.95 kg., were shaved. Six rabbits received mepivacaine 1.0 per cent, and 6, lidocaine 1.0 per cent, subcutaneously. The sites of injection during each experiment were alternated in the following sequence: right shoulder, left hip, left shoulder, and right hip. Beginning with a test dose of 20 mg./kg. of body weight, the dose was increased by 4 mg./kg. every 30 minutes until convulsions appeared or the animal died. Between injections the animals were observed for opisthotonos and/or convulsions.

Accepted for publication August 10, 1961. The authors are in the Division of Anesthesia, Duke University Medical Center, Durham, North Carolina.

*Group 2.* It was believed important to determine if the toxic dose of mepivacaine or lidocaine found by repeated injections at half hour intervals was an accurate reflection of each dose alone, or if the toxic level was a reflection of drug accumulation.

Using the technique described above, groups of 6 rabbits received mepivacaine 1 per cent or lidocaine 1 per cent subcutaneously, but only a single dose of the drug was injected on any one day, and then the animal was watched for signs of central nervous system irritation.

*Results.* With mepivacaine, opisthotonos and/or convulsions appeared after the administration of 32 mg./kg. in the majority of group 1 rabbits, while in group 2 a dose of 40 mg./kg. was required to produce the same signs.

In the lidocaine series a dose of 28 mg./kg. produced opisthotonos and/or convulsions in the majority of animals in both groups 1 and 2.

*Interpretation.* The method of Litchfield and Wilcoxon<sup>2</sup> was employed in the statistical analysis of these data. In group 1 the  $TD_{50}$  for lidocaine was 28 mg./kg. (25 to 31 mg./kg.)\* and the  $TD_{50}$  for mepivacaine was 32.4 mg./kg. (30.6 to 34.2 mg./kg.)\* However, the slope of the dose response curves for these two drugs were different and could not be compared.

In group 2 the  $TD_{50}$  for lidocaine was 28 mg./kg. (23 to 34 mg./kg.)\* and the  $TD_{50}$  for mepivacaine was 36 mg./kg. (30 to 44 mg./kg.)\* The difference between the drugs was not statistically significant.

The dose response curves were much steeper in group 1, and this probably was a reflection of drug accumulation.

Others<sup>3, 4, 5</sup> have determined the subcutaneous toxicity for mice, guinea pigs, and rabbits. Their studies indicate that mepivacaine was intermediate between procaine and lidocaine with regard to toxicity. On the other hand, Truant and Wielding<sup>6</sup> have reported

\* 95 per cent confidence limits.

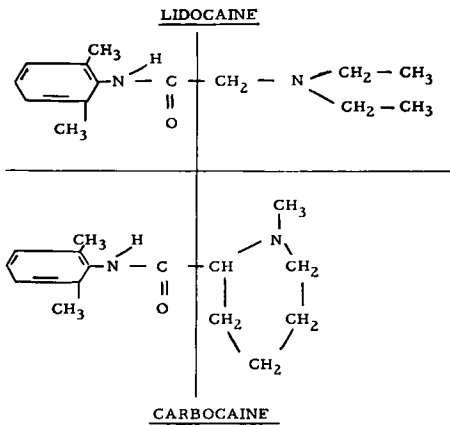


FIG. 1. Chemical structure of mepivacaine (below) and lidocaine (above).

that mepivacaine in mice is more toxic than lidocaine.

(2) INTRAVENOUS TOXICITY IN DOGS

*Method: Group 1.* Four mongrel dogs, weighing 5 to 13 kg., were anesthetized with thiamylal 20 to 25 mg./kg. During the experiment, N<sub>2</sub>O:O<sub>2</sub> in a 4:2 ratio was administered via a non-rebreathing endotracheal technique. Blood pressure (via femoral artery), electrocardiogram and electroencephalogram were recorded. When the dog had almost recovered from the effects of the thiamylal, serial injections of increasing doses of the local anesthetic drugs were administered at 5-minute intervals via the femoral vein. The initial dose was 4 mg./kg. If and when respiratory depression occurred, artificial respiration was

provided by means of a Palmer pump. Each dog served as his own control in that mepivacaine was administered one day and then a similar experiment was conducted with lidocaine 5 to 7 days later.

*Group 2.* To determine whether the preliminary administration of thiamylal might interfere with the manifestations of the local anesthetic drugs, 5 other dogs were prepared as above, except that the preliminary procedures were conducted using succinylcholine 0.5 mg./kg. and N<sub>2</sub>O:O<sub>2</sub> for muscle paralysis and anesthesia. A cuffed intra-tracheal tube was inserted immediately after the administration of succinylcholine, and artificial respiration was maintained. After completion of the preliminary procedures and resumption of normal respiratory activity, the serial injections of the local anesthetics were begun. As in group 1, each dog served as his own control.

The end point of each experiment was the appearance of marked depression of the electroencephalogram or clinical evidence of sustained generalized convulsions.

*Results: Tables 1 and 2. Group 1.* With both mepivacaine and lidocaine, apnea occurred with the greatest dose given—16 mg./kg. No significant changes in the electrocardiogram were noted with either drug at any dose level. However, in the electroencephalogram high-voltage waves superimposed on fast activity appeared with the smaller doses of both drugs. With higher doses, this activity was superseded by patterns indicative of cerebral depression and culminated in typical

TABLE 1  
INTRAVENOUS TOXICITY IN DOGS WITH PRIOR ADMINISTRATION OF THIAMYLAL SODIUM

|                        | Carboaine with Thiamylal *<br>(4 Dogs) |           |              | Lidocaine with Thiamylal *<br>(4 Dogs) |              |              |
|------------------------|----------------------------------------|-----------|--------------|----------------------------------------|--------------|--------------|
|                        | 4 mg./kg.                              | 8 mg./kg. | 16 mg./kg.   | 4 mg./kg.                              | 8 mg./kg.    | 16 mg./kg.   |
| Blood Pressure Fall    | 4                                      | 4         | 4            | 4                                      | 4            | 4            |
| Respiratory Depression | 0                                      | 0         | 4<br>(Apnea) | 0                                      | 1<br>(Apnea) | 4<br>(Apnea) |
| High Voltage Waves     | 2                                      | 3         | —            | 4                                      | —            | —            |
| Burst Suppression      | 0                                      | 1         | 4            | 0                                      | 4            | 4            |
| Twitching              | 0                                      | 0         | 1            | 0                                      | 0            | 0            |
| Clinical Convulsions   | 0                                      | 1         | 0            | 0                                      | 0            | 0            |

\* The numbers in the columns refer to number of animals showing reaction at that particular dosage.

TABLE 2

INTRAVENOUS TOXICITY IN DOGS WITH PRIOR ADMINISTRATION OF SUCCINYLGOLINE AND N<sub>2</sub>O:O<sub>2</sub>

|                        | Carbocaine with Succinylcholine *<br>(5 Dogs) |              |              | Lidocaine with Succinylcholine *<br>(5 Dogs) |              |            |
|------------------------|-----------------------------------------------|--------------|--------------|----------------------------------------------|--------------|------------|
|                        | 4 mg./kg.                                     | 8 mg./kg.    | 16 mg./kg.   | 4 mg./kg.                                    | 8 mg./kg.    | 16 mg./kg. |
| Blood Pressure Fall    | 1                                             | 1            | 0            | 1                                            | 2            | 1          |
| Respiratory Depression | 0                                             | 1<br>(Apnea) | 1<br>(Apnea) | 1<br>(Apnea)                                 | 2<br>(Apnea) | 0          |
| High Voltage Waves     | 2                                             | 2            | 1            | 2                                            | 3            | —          |
| Burst Suppression      | 0                                             | 2            | 1            | 1                                            | 1            | 3          |
| Rigidity or Twitching  | 0                                             | 2            | 0            | 1                                            | 2            | 0          |
| Clinical Convulsions   | 0                                             | 1            | 2            | 1                                            | 1            | 3          |

\* The numbers in the columns indicate the number of animals showing reaction at that particular dosage.

burst-suppression records. Clinical signs of convulsant activity occurred on only two occasions, both times with mepivacaine. A reduction of blood pressure, the degree dependent upon the dosage of local anesthetic given, occurred with each animal.

*Group 2.* In this group reductions in blood pressure were less frequent and less severe. Apnea was not seen as frequently, but when seen, it occurred with smaller doses of either drug. Again, no significant changes were noted in the electrocardiogram; the electroencephalogram showed patterns similar to the dogs in group 1 with increasing doses. The main difference in this group was that the majority of animals showed extensor rigidity, twitching of the extremities, or generalized convulsions with the larger doses of both drugs. These reactions were more obvious with lidocaine.

*Interpretation.* In this study the intravenous toxicity in dogs appeared to be equivalent for mepivacaine and lidocaine. Certainly no great difference between the two drugs was obvious. It should be noted, however, that previous administration of a barbiturate (even though its effects appeared to be worn off) masked certain central nervous system reactions of both mepivacaine and lidocaine.

Ulfendahl<sup>4</sup> reported in dogs a TD<sub>50</sub> intravenous dose of 7.2 mg./kg. for mepivacaine, 2.6 mg./kg. for lidocaine, and 3.7 mg./kg. for procaine. He was unable to offer any explanation for the relatively low toxicity of mepivacaine.

(3) NERVOUS TISSUE TOXICITY

*Method.* Twenty-six rabbits were anesthetized by open drop ether with the insufflation of oxygen. Using a sterile technique, the right and left sciatic nerves were exposed. In one series of 15 animals 0.25 ml. of lidocaine and mepivacaine in concentrations of 0.5, 1.0, 1.5 and 2.0 per cent were injected directly into the right and left sciatic nerves respectively. In a second series, 3 animals received 0.25 ml. mepivacaine 4.0 per cent directly into both sciatic nerves. In a control series of 3 animals, 0.25 ml. of normal saline was injected directly into both sciatic nerves. In a fourth series of 5 animals, 1.0 ml. of the test drugs were deposited around the nerve utilizing the same concentrations. All animals except the controls had a satisfactory sciatic nerve block as evidenced by hind leg paralysis on recovery from the ether anesthesia. The rabbits were sacrificed on the second, fourth or eighth day following injections, and the sciatic nerves were excised and prepared for histologic examination utilizing hematoxylin and eosin, Luxol fast blue and Masson trichrome staining techniques.

*Results.* In none of the microscopic sections of sciatic nerves which were exposed to the 0.5 through the 2.0 per cent concentrations of drugs was there evidence of nerve damage (myelin and/or axon degeneration). No demonstrable difference was noted between nerves blocked with lidocaine and those blocked with mepivacaine. The usual reaction seen in these sections was a connective tissue

TABLE 3

DURATION AND LEVEL OF SPINAL ANALGESIA IN  
DOGS ADMINISTERED MEPIVACAINE 30 MG.  
(1.5 ML. OF 2.0 PER CENT SOLUTION)

|        | Duration                       |                                  | Level of Anesthesia |
|--------|--------------------------------|----------------------------------|---------------------|
|        | Right Hind Leg<br>(in Minutes) | Left Hind<br>Leg (in<br>Minutes) |                     |
| Dog 1  | Not determined                 | 70                               | T-8                 |
| Dog 2  | Not determined                 | 60                               | Not determined      |
| Dog 3* | 170                            | 120                              | T-7                 |
| Dog 5* | 113                            | 83                               | T-5                 |
| Dog 6  | 85                             | 85                               | T-1                 |
| Dog 7  | 75                             | 73                               | T-2                 |

\* Spinal cord and membranes taken for microscopic sections on second day following spinal.

proliferation which was believed to be caused by the trauma of surgery or the injection, and which did not differ markedly from the controls. Nerve degeneration was seen in the right sciatic nerves of 2 of the 3 rabbits who received mepivacaine 4.0 per cent in both sciatic nerves. This reaction was noted in the rabbits sacrificed on the fourth and eighth days.

*Interpretation.* In 0.5, 1, 1.5 and 2.0 per cent concentrations, mepivacaine and lidocaine did not produce degenerative changes in the sciatic nerves of the rabbits. The reactions seen with these concentrations differed little from those seen in the saline controls, except the perineural reaction tended to be greater. Moreover, there was no difference in the reaction observed microscopically when the drug was injected directly into the nerve or when the nerves were bathed in the drug solutions. However, the results obtained indicated the mepivacaine 4.0 per cent probably was toxic to peripheral nerve tissue.

#### (4) TOXICITY IN MUSCLE TISSUE

*Method.* Two ml. of the test drugs were injected into the biceps femoris muscle of 6 rabbits. Each animal received lidocaine 1.0 or 2.0 per cent concentrations without epinephrine in the right hind leg and mepivacaine (same concentrations) in the left hind leg. Animals were sacrificed on the second, fourth and eighth days following injection, and sec-

tions of the muscle were taken for histologic examination.

*Results.* All muscle sections showed either no tissue reaction or minimal reaction on microscopic study. The minimal reaction consisted of scattered areas of sarcolemma proliferation.

*Interpretation.* One may conclude that neither mepivacaine nor lidocaine produced significant reactions in the muscle tissue of rabbits. However, Burn<sup>8</sup> found in rabbits that both mepivacaine and lidocaine injected intradermally in concentrations of 0.5 to 2.0 per cent caused atrophy of the muscular cutaneous maximus.

On the other hand, when injections into rabbit ears were performed, Truant and Wiedling<sup>6</sup> could establish no difference in local irritating effect between mepivacaine and lidocaine. Dhuner *et al.*<sup>9</sup> reported that there were no tissue changes in the rabbit's ear until a concentration of 8.0 per cent mepivacaine was reached.

#### (5) SPINAL ANESTHESIA IN DOGS

*Method.* Using essentially the technique of Wagner *et al.*,<sup>7</sup> and under thiopental anesthesia, 6 dogs were administered mepivacaine 30 mg. (1.5 ml. of 2.0 per cent solution) intrathecally, and 3 dogs received tetracaine 7.5 mg. diluted to 1.5 ml. with normal saline. Following administration the animals were kept in the right lateral decubitus position, and were not moved for 20 minutes, except to elevate the head. Observations were made on the duration of anesthesia in both the right and left hind extremities; an arbitrary end point was reached when the dog moved his hind limb in response to a painful stimulus applied to the hind paw. The level of spinal analgesia was determined by pinching the skin overlying the vertebral column with a hemostat; the level at which the skin would retract involuntarily was judged to be the height of analgesia. Two dogs were sacrificed on the second day following the subarachnoid block with mepivacaine, and the spinal cord with its membranes was removed for histologic examination.

*Results: Tables 3 and 4.* With mepivacaine 30 mg., the average duration of spinal anal-

gesia in the right hind extremity (the "down" side) was 110 minutes (75 to 170 minutes). In the left hind extremity the average duration was 80 minutes (60 to 120 minutes).

The average duration of analgesia with tetracaine 7.5 mg. was 161 minutes (135 to 200 minutes) in the right hind extremity, and 143 minutes (135 to 150 minutes) in the left hind extremity.

All dogs recovered completely from the spinal anesthetic, with no apparent residual effects. One of the spinal cords examined histologically was entirely normal. The other cord showed grossly an area of erythema at the point of insertion of the needle; microscopically, an inflammatory cellular reaction was noted in this area. This reaction was interpreted as being due to direct trauma to the spinal cord by the spinal needle.

*Interpretation.* Moderately prolonged and apparently satisfactory spinal analgesia was obtained in dogs with mepivacaine 30 mg. Full recovery of function occurred without detectable residual effect, and without evidence of spinal cord damage histologically other than that which could be attributed to the needle puncture.

Ludena *et al.*,<sup>5</sup> when they produced spinal analgesia in rabbits with mepivacaine 2.0 per cent, found that urethral anesthesia lasted an average of 31 minutes without residual effects. However, when they used 4.0 and 8.0 per cent solutions, the incidence of residual effects was 19 and 50 per cent respectively.

(6) DURATION OF ACTION

*Method.* A total of 24 rabbits were prepared by direct exposure of the sciatic nerve under open drop ether anesthesia. The right

TABLE 4

DURATION AND LEVEL OF SPINAL ANALGESIA IN DOGS ADMINISTERED TETRACAINE 7.5 MG. (1.5 ML. OF 0.5 PER CENT SOLUTION)

|       | Duration                    |                            | Level of Anesthesia |
|-------|-----------------------------|----------------------------|---------------------|
|       | Right Hind Leg (in Minutes) | Left Hind Leg (in Minutes) |                     |
| Dog 4 | 135                         | 135                        | T-7                 |
| Dog 8 | 150+                        | 150                        | T-1                 |
| Dog 9 | 200+                        | 145                        | Not determined      |

TABLE 5  
DURATION (IN MINUTES) OF SCIATIC NERVE BLOCK IN RABBITS COMPARING MEPIVACAINE AND LIDOCAINE

| Drugs                                             | Number of Rabbits | Arithmetic Mean | Standard Deviation |
|---------------------------------------------------|-------------------|-----------------|--------------------|
| Mepivacaine 1 per cent                            | 6                 | 58.4            | ± 9.6              |
| Lidocaine 1 per cent                              | 6                 | 54.6            | ± 8.6              |
| Mepivacaine 1 per cent with 1:200,000 epinephrine | 6                 | 85.8            | ±22.2              |
| Lidocaine 1 per cent with 1:200,000 epinephrine   | 6                 | 112.5           | ±34.6              |
| Mepivacaine 2 per cent                            | 6                 | 70.8            | ±15.3              |
| Lidocaine 2 per cent                              | 6                 | 59.2            | ± 5.85             |
| Mepivacaine 2 per cent with 1:200,000 epinephrine | 6                 | 114.1           | ±35.04             |
| Lidocaine 2 per cent with 1:200,000 epinephrine   | 6                 | 102.5           | ±29.3              |

sciatic nerve was bathed with 1 ml. lidocaine, while the left sciatic was exposed to 1 ml. of mepivacaine. Care was taken not to disturb the fascia overlying the nerve: the solutions were injected under the fascia adjacent to the nerve. The drug concentrations used were 1.0 and 2.0 per cent with and without 1:200,000 epinephrine. Six rabbits were utilized for each type of mixture.

*Results: Table 5.* The average duration of anesthesia with lidocaine 1.0 per cent and mepivacaine 1.0 per cent without epinephrine was 54 minutes (43 to 65 minutes) and 58 minutes (45 to 70 minutes) respectively. When epinephrine was added, the average for lidocaine was 112 minutes (80 to 145 minutes), and for mepivacaine was 85 minutes (60 to 120 minutes).

With concentrations of 2.0 per cent, lidocaine without epinephrine had an average action of 59 minutes (55 to 65 minutes), and mepivacaine was effective for an average of 70 minutes (45 to 85 minutes). When 1:200,000 epinephrine was added, the average time of action for lidocaine was 102 minutes (80 to 160 minutes), and for mepivacaine was 114 minutes (60 to 160 minutes).

*Interpretation.* None of the above results, when analyzed statistically, proved to be significant. In rabbits both mepivacaine and lidocaine, with and without the addition of epinephrine, produced sciatic nerve blocks of comparable duration.

However, Henn<sup>3</sup> in his studies concluded mepivacaine was more effective than lidocaine when tested for corneal anesthesia in the rab-

bit, for infiltration anesthesia in guinea pigs and man, and for conduction anesthesia of various types in man. But when epinephrine was added, the difference between mepivacaine and lidocaine was not always significant.

When used for retro-bulbar injections in man, Boberg-Ans<sup>10</sup> found that the duration of corneal anesthesia obtained with mepivacaine was approximately 2 times that obtained with lidocaine.

In skin wheal tests Dhuner *et al.*<sup>9</sup> found mepivacaine gave longer anesthesia than lidocaine; but on adding epinephrine to the drugs, the duration was about the same. Ekenstam<sup>1</sup> *et al.* reported similar results. Ulfendahl<sup>4</sup> indicated that mepivacaine had a longer duration of action than lidocaine when used for local infiltration in mouse tails and for finger blocks in man.

#### CLINICAL STUDIES

Mepivacaine without epinephrine was employed for 264 regional nerve blocks. In 222 patients surgical procedures were performed and in 42 patients the drug was administered for diagnostic and therapeutic purposes. The majority of these blocks were performed by the resident staff under supervision, and commonly accepted techniques were utilized. Included were 17 types of regional block.

*Dosages Employed.* Concentrations of 0.5, 1.0, 1.5 and 2.0 per cent solutions were employed. For subcutaneous infiltration 0.5 per cent was adequate. To block both sensory and motor functions of larger nerve roots, either 1.5 or 2.0 per cent solutions were required. In two patients, in whom a 1.0 per cent solution was used for epidural analgesia, satisfactory muscular relaxation could not be obtained.

The highest single dose employed was 700 mg. in a 1.0 per cent concentration for a bilateral multiple intercostal nerve block in a 65 year old male. This dosage was tolerated without complication. Frequently, single doses of 500 to 600 mg. were utilized without incident. During continuous lumbar epidural block, the highest dose administered was 1,300 mg. (1.5 per cent solution) over a period of four hours and ten minutes. With this technique of analgesia, usually 200 to 220 mg. of drug were sufficient to establish analgesia, and

increments of 100 mg. at 30 to 45-minute intervals provided a smooth course of anesthesia.

*Onset of Action.* With a well-performed nerve block, the onset of analgesia was rapid. Within 5 minutes of completing the injections, preparation of the operative area could begin. Profound analgesia and muscular relaxation was present within ten minutes.

*Adequacy and Duration of Action.* Unless the situation demanded, hypnotic drugs such as thiopental were not administered to "cover" the regional block. Therefore, a fair estimate could be made of the adequacy and duration of action. In 18 patients (6.8 per cent) incomplete analgesia was obtained, primarily because of improper techniques, and supplementation with other drugs was required from the beginning of operation. In 9 patients, all undergoing laparotomy following intercostal block, nitrous oxide and oxygen, or ethylene and oxygen, in a 50:50 ratio, were administered to reduce peritoneal reaction. In these patients no other supplementation was required, so it was believed that the regional block was adequate. (This technique was reserved for poor risk, elderly patients undergoing laparotomy.)

In 7 other patients (2.5 per cent) the block failed to outlast the period of operation, and for this reason supplementation was required. Four patients required reinforcement of analgesia after one and a half hours, 2 patients after two and a half hours, and one after three and three-fourths hours. As a general rule, adequate analgesia could be counted on for a minimum of one and a half hours; frequently it persisted for three hours. The longest noted analgesic action was five and a half hours, following a sciatic-femoral block with 2.0 per cent solution. Since the total number of partial failures was only 6.8 per cent, and since the blocks were being performed by residents-in-training, it was concluded that this drug possessed a satisfactory diffusibility which enhanced its efficacy.

*Complications.* Complications associated with mepivacaine injection *per se* were few in number. Burning sensations and discomfort were seldom associated with intradermal, subcutaneous or intramuscular injections. In one patient who received 20 ml. of 2.0 per cent mepivacaine (400 mg.) for a combined right

cervical and supraclavicular brachial plexus block, unconsciousness supervened for one and a half minutes about five minutes after the final injection. Accompanying the loss of consciousness was a slowing of the pulse rate, but the blood pressure and respiratory rate remained unchanged. The only definitive therapy applied was the administration of oxygen.

Two elderly patients who received 300 and 400 mg. of mepivacaine for a regional block in preparation for inguinal herniorrhaphy each developed moderate hypotension (40 mm. of mercury fall) 10 to 20 minutes after completion of the block. Both patients responded favorably to vasopressor drugs and required no other specific therapy except the administration of oxygen.

One death occurred in this series. A 68 year old male, with a history of coronary infarction eight years previously, received mepivacaine 250 mg. via the caudal route for excision of a fissure-in-ano. Analgesia was satisfactory, vital signs remained normal during the 45 minutes he was in the operating room, and the level of consciousness (that allowing normal conversation) had not altered when the patient was returned to the recovery room. However, at this time he was noted to be groggy and exhibited a Cheyne-Stokes respiration. These reactions were attributed to the meperidine-levallorphan intravenous drip solution (50 mg. meperidine) which he had received during operation. Thirty minutes after return to the recovery room the patient's condition deteriorated rapidly; blood pressure could not be obtained, respirations were rapid and shallow, and the clinical picture resembled shock. Electrocardiogram at this time showed changes, when compared to the preoperative tracing, indicative of "some catastrophe or coronary occlusion." In spite of all efforts, the patient died one hour later. At autopsy the left myocardium, in almost its entirety, was markedly thinned and scarred, and both the left and right coronary vessels were almost completely occluded.

#### DISCUSSION

The investigations described above have indicated that the toxicity of mepivacaine, when administered subcutaneously or intravenously,

is comparable to that of lidocaine. The range between doses which produce satisfactory analgesia and those which produce systemic toxic reactions is sufficiently wide that one may conclude that clinical administration would be safe.

Histologic studies of the sciatic nerve and muscle tissue in the rabbit have shown that the local irritative reaction associated with mepivacaine in concentrations used clinically is minimal, and no greater than that observed with lidocaine. No permanent damage to the sciatic nerve of rabbits exposed to mepivacaine in concentrations of 1.0 and 2.0 per cent was noted histologically. It is suggested that mepivacaine fulfills the requisites of a useful local anesthetic drug in that it neither induces severe, local tissue reactions at the site of injection, nor produces irreversible changes in the nerves to which it is exposed.

It is of some importance in present-day surgery that a local anesthetic drug combine an absence of local tissue reaction with as long a blocking action on the nerves affected as possible. To delay the absorption of the local anesthetic drug, and thus to enhance its efficacy, epinephrine traditionally has been added to the local anesthetic solution. However, epinephrine itself may have generalized undesirable systemic actions, particularly in the geriatric patient. Therefore, it would be of interest to find a drug which would exert a reasonably long-lasting, yet reversible action without the addition of epinephrine. The durations of action of lidocaine and mepivacaine were similar in this study, and we were not able to confirm the results of other investigators<sup>3, 4, 9</sup> employing different species, who found that mepivacaine without epinephrine had a longer duration of analgesia than lidocaine with epinephrine.

Spinal analgesia with mepivacaine in dogs was compared with that produced by tetracaine because the latter drug has proved so useful clinically in this respect. The results in dogs suggest that mepivacaine is not superior to tetracaine, primarily because its duration of action is shorter. In the two dogs whose spinal cords were examined histologically following subarachnoid injection of mepivacaine, no lesions attributable to the drug were found.

The clinical experiences with mepivacaine have borne out the observations made in animals. Systemic side reactions have been few, to the extent that we believe it safe to administer dosages up to 500 mg. at one time without added epinephrine except in extremely vascular areas.

#### SUMMARY

Systemic toxicity of mepivacaine in rabbits following subcutaneous administration was no greater than that seen with lidocaine. Systemic toxicity of mepivacaine in dogs following intravenous administration was equivalent to that found with lidocaine.

Local reactions in the sciatic nerves of rabbits following exposure to mepivacaine was minimal and similar to that seen with lidocaine. Local reactions in muscle tissue of rabbits were minimal following mepivacaine injections.

Adequate, reversible spinal analgesia was observed in dogs following subarachnoid injection of mepivacaine. The duration of analgesia with mepivacaine following sciatic nerve block in rabbits was comparable to that seen with lidocaine.

A clinical evaluation of 264 patients showed that regional nerve block analgesia produced by mepivacaine without added epinephrine was effective for periods from one and one-half to six hours.

The study was supported in part by a grant from Winthrop-Stearns.

#### REFERENCES

1. Ekenstam, B., Egner, B., Ulfendahl, H. R., Dhuner, K. G., and Oljehund, O.: Trials with Carbocaine, *Brit. J. Anaesth.* **28**: 503, 1956.
2. Litchfield, J. T., and Wilcoxon, F.: Simplified method of evaluating dose-effect experiments, *J. Pharmacol. Exp. Ther.* **96**: 99, 1949.
3. Henn, F.: Determination of toxicological and pharmacological properties of Carbocaine, lidocaine and procaine by means of simultaneous experiments, *Acta Anaesth. Scand.* **4**: 125, 1960.
4. Ulfendahl, H. R.: Some pharmacological and toxicological properties of new local anaesthetic, Carbocaine, *Acta Anaesth. Scand.* **1**: 81, 1957.
5. Ludena, F. P., Hoppe, J. O., Coulston, F., and Drobeck, H. P.: Pharmacology and toxicology of mepivacaine, new local anesthetic, *Toxicol. Appl. Pharmacol.* **2**: 295, 1960.
6. Truant, A. P., and Wieding, Sten: Contribution to pharmacological and toxicological evaluation of new local anaesthetic, d,l-methylpipercolyl-2, 6-xylylide. *Acta Chir. Scand.* **116**: 351, 1959.
7. Wagner, J. C., Sievers, R. F., Bennett, A. L., McIntyre, A. R.: Spinal anesthesia in dogs, *J. Pharmacol. Exp. Ther.* **68**: 437, 1940.
8. Brun, A.: Effect of procaine, Carbocaine and Xylocaine on cutaneous muscle in rabbits and mice, *Acta Anaesth. Scand.* **3**: 59, 1959.
9. Dhuner, K. G., Oljelund, O., and Aagesen, G.: Carbocaine-d,l-N-methylpipercolic acid 2, 6-dimethylanilide—new local anesthetic agent, *Acta Chir. Scand.* **113**: 350, 1957.
10. Boberg-Ans, J.: Comparison of effect of two local analgesics, *Nord. Med.* **60**: 1361, 1958.