# MONOCAINE FORMATE: ITS APPLICATION IN SPINAL ANESTHESIA *

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MONOCAINE hydrochloride † (mono isobutyl amino ethyl para amino benzoate hydrochloride), an isomer of procaine, was synthesized by Goldberg in 1935 (1). After investigating several compounds which might combine anesthetic and vasoconstrictor properties, Goldberg and Whitmore in 1937 (2), and Abramson and Goldberg in 1938 (3) reported that monocaine was an effective local anesthetic, with a low toxicity and with an increased rapidity of action as compared with procaine.

## USE IN DENTAL ANESTHESIA

Monocaine was released to the dental profession in 1937. Since then it has had an increasing popularity as an agent for conduction anesthesia in dentistry. Hyatt (4), Nevin (5), Rosado (6), Sweeney (7), Adelman (8), and others have reported favorably upon the clinical application of the drug in this field. Their reports were in general agreement that adequate anesthesia is produced more rapidly with monocaine solutions and frequently to a greater degree than with procaine; the duration of the anesthesia is increased; the drug is synergistic with epinephrine; toxic reactions in the form of the so-called "jitters" are minimized or eliminated; the symptoms of onset and disappearance of anesthesia are less pronounced and unpleasant; disturbing postoperative effects are not observed. Tainter and Throndson (9) utilized 251 patients to compare the anesthetic efficiency of monocaine and procaine as local anesthetic agents in oral surgical procedures. Their observations were not in complete agreement with those of the authors cited above. Using 2 per cent procaine with 1:50,000 epinephrine to compare with 1 per cent monocaine with 1:75,000 epinephrine, both dissolved in a sodium chloride solution containing 0.1 per cent sodium bisulphite, they found that the average volume required for anesthesia was about the same for both solutions; the onset of anesthesia was nearly identical; the minor untoward reactions were of equal frequency with the two solutions; the changes in circulation and respiration were similar, though minor with both solutions; the tissue irritation was greater with monocaine. They did find, how-

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ever, that the duration of anesthesia with 1 per cent monocaine was definitely longer than with 2 per cent procaine, and that 1:75,000 epinephrine in 1 per cent monocaine produces substantially the same degree of vasoconstriction as 1:50,000 epinephrine in 2 per cent procaine. It was suggested by the authors that these properties are not of too much importance in dental anesthesia. That is a point for the dental clinician to decide, but in surgical anesthesia the duration of anesthesia with drugs of comparable toxicity, and vasoconstriction with decreased epinephrine do have a definite significance.

Brenner submitted the first report upon the use of monocaine solution for anesthesia outside of the dental field. Proctological and rectal procedures were completed satisfactorily (10). Meyersburg obtained excellent results while using it as a local anesthetic agent during more than four thousand tonsillectomies (11).

## LABORATORY STUDIES

Monocaine has been investigated as an anesthetic agent for laboratory animals by others since the original reports of Goldberg and his co-workers (2, 3) who concluded it was "a very effective drug for infiltration and conduction anesthesia, more toxic than procaine but with an anesthetic efficiency many times greater." Butts and Koelle (12), in an extensive study with different species of laboratory animals, concluded in an epitomized report that monocaine was less toxic than procaine; that it was synergistic with epinephrine; that it produced no grave tissue changes; that it gave significantly greater depth and duration of anesthesia than could be produced with similar concentrations of procaine. Schamp et al. (13) reported that from animal experiments "Monocaine had no significant advantage over procaine as indicated by concentration of solution required for speed of onset or duration of anesthesia." One of the authors had found previously from clinical use a longer duration of anesthesia with monocaine (9).

Reviewing the pharmacological studies it seemed apparent that the difference of opinion expressed by the several investigators arose essentially from methods of study, variation of species and interpretation of data. No laboratory investigation supplied any evidence that would preclude an extensive clinical trial of monocaine for the several types of surgical anesthesia completed with local anesthetic agents. Moreover, from the laboratory data collected most experiments indicated that the drug had certain definite advantages over procaine. Therefore, an investigation was undertaken to aid in evaluating monocaine in surgical anesthesia. The final appeal of any anesthetic agent is to its utility during clinical surgery and its complete effects on man.

Duration is of paramount importance in spinal anesthesia. Since the available evidence indicated that in comparable doses monocaine was effective for a longer time than procaine, the initial clinical investigation here was directed toward its application in spinal anes-

thesia. Monocaine hydrochloride is soluble in water to the extent of 3 per cent. Concentrations regularly used for spinal anesthesia vary according to individual anesthetists from 2½ to 10 per cent. To secure this range of solubility with monocaine, the formic acid salt, which is soluble in any dilution needed clinically, was used instead of the hydrochloride.

Monocaine formate occurs as white crystals which are readily soluble in spinal fluid and stable in solution. It can be sterilized by boiling or autoclaving and is not affected by sunlight. Solutions of 5 and 10 per cent, made with sterile water, normal saline and spinal fluid, respectively, were vigorously agitated and exposed to air for forty-eight hours without evidence of change. The drug has been found to have bacteriocidal properties. Comparing equal concentrations, it is one-seventh as bacteriostatic as phenol. Using the F.D.A. agar plate method and testing against Staphylococcus aureus, it showed inhibitory powers at concentrations starting at 1.5 per cent. With the solution tested, ½ to 4 per cent in sterile beef extract broth, no growth was produced after sixteen days of incubation (37 C.) (14).

## CLINICAL STUDIES

This clinical study was preceded by an investigation of monocaine formate spinal anesthesia in animals (rabbits, cats) in the experimental surgical laboratories here (15). It was shown to be only half as toxic as procaine for rabbits, and slightly more toxic for cats. The sequence of symptoms following spinal injections was identical for procaine and monocaine. It was concluded from this study that "Monocaine formate, according to the criteria used, seemed as effective as, and safer than, procaine hydrochloride."

This report includes the first 307 consecutive cases of clinical anesthesias produced here with monocaine formate. It was proposed in the beginning to study in careful detail 300 patients to determine whether or not the drug merited further investigation. Being satisfied that a more extensive study should be completed, additional cases are being accumulated rapidly.

Patients were chosen indiscriminately without considering the operation, the only criterion being that spinal anesthesia was to be employed. Spinal anesthesia for thoracic surgery was not done during the time of this study. There was a preponderance of males over females because of the higher incidence of surgical procedures on males where spinal anesthesia was the method of choice. Classification of patients according to physical status placed 195 in group one, 74 in group two, 17 in group three, 2 in group four, 18 in group five and 1 in group six. Evaluation of the physical status of patients was based upon the classification accepted by the American Society of Anesthetists, Inc.

In this classification the physical condition of the patient is the only factor considered. It is not a grouping according to anesthesia or surgical risks. The complexity or duration of operation, ability of the surgeon and anesthetist, and the many other factors that enter into the risk of operation are disregarded. Group 1 includes patients with no organic pathology or for whom the existing pathology causes no systemic disturbance. The great majority of all surgical patients are in this group. In group 2 are those individuals with moderate systemic disturbances. Those in group 3 have severe systemic disturbances, and in those in group 4 the systemic disorders have become a serious threat to life. Patients who would ordinarily be placed in groups 1 and 2 who are done as emergencies are put in group 5 and those who fall in groups 3 or 4 are classified as group 6.

Age distribution in this series showed the greatest number of patients (81) to be in the fifth decade, although the average age was 38.4 years, with the youngest individual 16, the oldest 86. Morphine and scopolamine was the premedication of choice in the majority of instances, the dosage adjudged according to the individual patient. Demerol * in doses of 75 or 100 mg., with scopolamine 0.4 mg., was employed satisfactorily for 35 patients, while sodium pentobarbital, 0.1 Gm., with scopolamine 0.0004 Gm., was the preanesthetic medication for 14.

The technic for administration was that commonly employed for spinal anesthesia with procaine. With the patient in the lateral position on a level table, spinal puncture was completed through the third or fourth interspace using a 19 or 20 gage needle. Sufficient cerebrospinal fluid was withdrawn to make a solution of the desired concentration. The monocaine crystals were dissolved in their ampule, at room temperature, the solution aspirated into the syringe and then injected into the subarachnoid space. Two and one half, 5, 7½ and 10 per cent solutions were used. The 5 per cent solution was chosen for routine use. It was considered safe. Barbotage was not employed except as required when the technic of continuous spinal was used. Immediately upon withdrawal of the needle the patient was turned to the supine posture, unless another position was indicated by the anticipated surgery, and tested for skin levels of sensory anesthesia. With the first evidence of beginning anesthesia, preparation of the operative field was permitted. This was within two minutes, approximately, from the time of injection and the patients were ready for surgery upon the completion of draping. Blood pressure readings, the rate and character of the pulse and respiration, and the levels of sensory anesthesia were recorded at short intervals throughout surgery, and attention given to the general comfort of the patient.

During anesthesia for the first few cases it became obvious that the diffusion of monocaine in spinal fluid differed from that of procaine.

* Supplied by Alba Pharmaceutical Co., Inc.

The level of sensory anesthesia gradually extended cephalad, occasionally for as long as thirty minutes after injection. Frequently when the extent of anesthesia seemed to be fixed at a definite segment with no anesthesia demonstrated above that level after testing two or three times at three to five minute intervals, it would be noted at a higher level ten minutes later. To avoid having anesthesia reach undesirably high levels, monocaine was injected more slowly than is the practice here when procaine is used. It required very little experience to adjust the rate of injection so that the predictable level of anesthesia was regularly obtained. When 100 mg. is given for lower abdominal operations, an approximate rate of 1 cc. per fifteen seconds will give the desired anesthetic levels.

Ephedrine sulfate was not employed prophylactically but was used therapeutically in most cases when the systolic blood pressure fell to 90 mm. or below. With precipitous falls the customary procedure was to administer 24 mg. of ephedrine intravenously, followed by the same, or a 48 mg. dose intramuscularly ten minutes later if the initial dose failed to produce the desired result. Neosynephrine has been used in the same manner. Oxygen inhalations, with or without slight Trendelenburg posture, were resorted to frequently as supplemental therapy for hypotension. Satisfactory response to such treatment was obtained in all but 3 patients; none of whom had any subsequent unfavorable reaction. One with a blood pressure reaching 60/40 mm. Hg and two others where it was so low that it could not be obtained accurately were improved but the preanesthetic blood pressure levels were not recorded until surgery was completed and anesthesia receding. Ten patients with blood pressure determinations varying from 90/60 to 60/46 mm. Hg received no treatment. All showed a gradual and satisfactory recovery.

The technic of continuous spinal anesthesia (16) was used for 5 patients with spinal fluid as the drug solvent. The smallest amount of drug required was 80 mg. for a partial colectomy of two and one-quarter hours' duration; the most, 220 mg. for a gastrectomy requiring three and one-quarter hours of anesthesia. The results in these few cases compared favorably with similar ones in which procaine was given, the only essential difference being more prolonged anesthesia with each fraction injected.

The onset of anesthesia following subarachnoid injections of monocaine is very rapid. Rarely were more than three or four minutes required before surgery could be started. There was no need for delay between injection and surgery other than that occasioned by placing the patient in position and preparing the operative field. Sensory anesthesia was regularly obtained well in advance of motor paralysis. In 10 per cent of the cases the latter was entirely absent from the lower extremities with surface anesthesia at or above the level of the lumbar segments. When 50 mg. or less of the drug is used motor paralysis is

often absent or incomplete. In this respect anesthesia with monocaine resembles that with intracaine. Intercostal paralysis likewise was frequently absent when sensory anesthesia involved the upper thoracic segments. In 1 case, when skin anesthesia was noted in the area supplied by the lower cervical nerves and the recti were relaxed, the intercostal muscles were active. When motor function was lost or incomplete it returned regularly before sensory function was re-established.

The duration of anesthesia with monocaine was proportional to the amount of drug employed, although as the dosage was increased the time of anesthesia was not prolonged in direct ratio. The average duration when 50 mg. was given was seventy-five minutes; 100 mg. averaged ninety-eight minutes; 150 mg. produced satisfactory anesthesia for one hundred twenty minutes. These averages are definitely increased over those from procaine, particularly with the smaller doses, and somewhat increased over intracaine (17). Supplemental anesthesia was required for 9 patients (2.9 per cent). No anesthesia (technical error) was obtained in 1 of these, in 2 the extent of anesthesia would not permit the surgery involved, and in the others anesthesia was not of sufficient duration. Inhalation anesthesia with cyclopropane or nitrous oxide-oxygen was uneventful in these cases. It is interesting to note that in no instance was the surgeon able to determine whether monocaine or procaine was being used.

### COMPLICATIONS DURING ANESTHESIA

Circulatory complications were not significantly different from those encountered with procaine except that they were usually more gradual in development. Maximal hypotension occurred from ten to thirty minutes after anesthesia in the majority of cases and, in general, paralleled the above mentioned tendency for the drug to ascend to a level above that at which it seemed to be fixed initially. No significant falls in blood pressure occurred when levels of anesthesia were established at $T_{10}$ or below. In most cases there was a proportionately greater decrease in systolic than in diastolic pressure. Surgery was in progress regularly at the time arterial tension decreased. Twenty-eight per cent of the cases had some fall in blood pressure. The systolic pressure fell to 90 mm. Hg or less in 19.5 per cent. Classified on the basis of a severe fall in blood pressure (mean pressure decreased 40 per cent or more), 20 per cent were severe. Those listed as moderate (mean pressure decreased 20 to 39 per cent) totaled 7 per cent. It was noted that the majority of individuals with falls in blood pressure showed little change in pulse rate or quality. Four patients, each with a systolic decrease of 40 per cent or more, developed bradycardia.

Twenty patients had nausea, or nausea and emesis, during anesthesia. One-fifth of these occurred when abdominal traction was applied, the remainder during the time when hypotension was maximum. Cessation of traction or oxygen therapy effected relief. Syncope appeared in 1

patient whose blood pressure fell to 0/0. The response to treatment with ephedrine was prompt.

### POSTOPERATIVE COMPLICATIONS

Headache was a complication for 13 patients (4.2 per cent). One had a severe headache of ten hours' duration. Two complained of a heavy feeling only. Headache was sustained for less than twenty-four hours except for 3 patients, 2 of whom had a mild headache lasting two days and 1 for three days. Two patients became irrational, 1 an 83 year old uremic individual who became disoriented on the second postoperative day and remained so for approximately twenty-four hours. The other was an anemic 56 year old male who had a resection of the ascending colon for malignancy. The operation required two and three-quarters hours and was performed during continuous spinal anesthesia with 200 mg. of monocaine. The patient was irrational during the first 3 days postoperatively. Recovery was complete for both patients.

Urinary retention was a complication for 3.2 per cent of patients, one-half of these of one day's duration or less. Four patients had retention for two days, and in 1 it persisted for six days following a bilateral herniorrhaphy. Two patients had postoperative nausea and 2 had nausea and emesis. Peritonitis was a complication in 1 patient following partial colectomy.

Respiratory complications were diagnosed for 13 patients (4.2 per cent). They were: hiccough 2, cough 4, bronchitis 1, atelectasis 1, pulmonary edema 1, bronchopneumonia 2, lobar pneumonia 2. Eight occurred in urological patients in the upper age groups, 2 following gastric resections, 1 after cholecystectomy with choledochostomy and 2 following herniorrhaphies.

There were 5 deaths following monocaine spinal anesthesia giving a mortality of 1.6 per cent. No death occurred during anesthesia or was attributable directly to it. Primary causes of death were uremia, peritonitis, bronchopneumonia and pulmonary edema, all occurring in older, poor risk patients.

### SUMMARY

Pharmacological studies and early clinical reports on monocaine served to recommend its use in clinical anesthesia. It had been reported that with comparable amounts the duration of anesthesia with monocaine exceeds that from procaine; that monocaine is synergistic with adrenalin; that it is bacteriostatic; that it is not more toxic than procaine.

A preliminary study of 307 unselected patients who had spinal anesthesia with monocaine formate given by the standard or the continuous spinal technic is reported.

With the amounts used, 50 to 150 mg. in 5 per cent concentration in spinal fluid, the results observed during anesthesia and postoperatively

indicate that complications are no more severe and of lower incidence than might be expected from procaine.

Relatively smaller doses of monocaine are effective, the onset of anesthesia is more rapid and the duration comparatively longer than with procaine.

Monocaine diffuses more rapidly than procaine in spinal fluid. It should be injected more slowly. Motor paralysis following the subarachnoid injection of monocaine frequently is slower in onset and shorter in duration than sensory anesthesia.

Monocaine is judged, from this preliminary study, to be a useful and safe agent for spinal anesthesia when given in low concentrations and small or moderate doses.

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