ANESTHESIA XXXV. THE LOCAL ANESTHETIC ACTION OF METAHYDROXYPROCAINE *†

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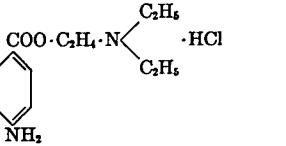
SINCE the synthesis of procaine by Einhorn in 1905 many compounds having analogous structures have been introduced into the practice of anesthesiology. Some of these substances have exhibited certain advantages over the action of procaine. Such compounds as tetracaine and butacaine have been demonstrated to have greater potency and to produce anesthesia of longer duration. In most instances, however, potency as a local anesthetic and systemic toxicity have paralled each other as properties of these agents, and procaine has remained one of the most generally used of all of the local anesthetic agents.

It is well established that the local anesthetic activity of procaine hydrochloride or related local anesthetic agents is augmented by the addition of sodium bicarbonate or other alkaline salts. It appears that the activity of the procaine base as a local anesthetic exceeds that of its soluble hydrochloride salt. Numerous attempts have been made to solubilize procaine base with slightly dissociated acids such as boric and carbonic acids (1). It occurred to us that the introduction of a phenolic hydroxyl group into the procaine molecule, producing an "orthoform type" compound, might provide the means of solubilizing the procaine type molecule as the free base. Accordingly, m-hydroxyprocaine was prepared by one of us (J. F. V.). Its relationship to procaine is apparent from the following formulas:



Procaine Hydrochloride

Sodium Salt of m-Hydroxyprocaine Base

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The m-hydroxyprocaine was prepared as its hydrochloride as a yellowish-white crystalline substance. It darkened upon exposure to air. For use in these studies 2 Gm. of the hydrochloride salt was dissolved in 14 cc. of tenth normal sodium hydroxide solution and made up to 100 cc. with 0.5 per cent solution of sodium bicarbonate. The pH of the 2 per cent solution of the compound was 7.8 at 25 C. as measured by the glass electrode. This solution probably is composed of the free base of m-hydroxyprocaine in a solution of some sodium salt of the compound buffered with bicarbonate.

LOCAL ANESTHETIC EFFICIENCY

The efficiency of m-hydroxyprocaine as a local anesthetic agent was studied using a 2 per cent solution of its sodium or potassium salt. Although the potassium ion was demonstrated by Kochmann to elicit local anesthetic action, we were unable to observe any advantage in the use of the potassium salt. This observation is in accord with the findings of Tainter (2). Comparisons were made with a 2 per cent aqueous solution of procaine hydrochloride.

Skin of Frog.—The Turck method was employed to determine the relative efficacies of the two solutions, procaine hydrochloride and m-hydroxyprocaine. Surface anesthesia was produced on the frog's foot by immersion in the agent and the time required to react to an irritant acid (0.5 per cent solution of hydrochloric acid) determined in the spinal animal. The reflex time for removal of the foot from the acid was markedly greater when m-hydroxyprocaine was used than when procaine hydrochloride was employed. In 9 frogs the reflex time with procaine hydrochloride was approximately eighteen seconds; with m-hydroxyprocaine it was approximately three minutes.

Cornea of Rabbit.—The conjunctivae of the rabbit were employed also to test the duration of anesthesia produced by procaine hydrochloride and m-hydroxyprocaine. In 15 rabbits the two solutions were instilled in the conjunctival sacs of the right and left eyes, respectively. The wink reflex was tested each ten minutes by means of a blunt glass rod employing the usual precautions. The end point for procaine hydrochloride was between ninety and 115 minutes; for m-hydroxyprocaine it was approximately 210 minutes.

In another series of 4 rabbits the sodium and potassium salts of m-hydroxyprocaine were tested, respectively, on the left and right eyes, but no significant difference in the duration of anesthesia was elicited.

Sciatic Nerve of Guinea Pig.—The relative efficiency of the two compounds in producing sciatic nerve block was determined by the technic suggested by Shackell (3). Six animals were used for each compound. The average duration of the block with procaine hydrochloride was fifteen minutes; with m-hydroxyprocaine the time of block averaged twenty-three minutes.

Sciatic Nerve of Dog.—A dog under ether anesthesia was set up for blood pressure recording in the usual manner. Each sciatic nerve was exposed. The threshold faradic stimulus necessary to produce vasomotor effects was determined. Procaine hydrochloride and m-hydroxyprocaine, 0.1 cc., were injected, respectively, into the right and left sciatic nerve trunks. Nerve block to faradic stimulation was produced by each compound and the duration of block was approximately the same.

Intradermal Wheal in Man.—Intracutaneous wheals were produced in the skin of the flexor surface of the forearm of 6 subjects by injecting 0.1 cc. each of the anesthetic solutions. The wheals were tested for perception by the von Frey bristle. With threshold tests for anesthesia and tests for duration of anesthesia, each compound appeared to be equally potent.

Spinal Anesthesia in Dog.—Ten dogs received 2 cc. of m-hydroxyprocaine, 4 per cent intrathecally, in the seventh lumbar interspace. Anesthesia ensued within five minutes and lasted approximately ten minutes. The anesthetic syndrome appeared to be comparable to that of procaine hydrochloride administered under the same conditions.

TOXICITY STUDIES

Intravenous Administration in Rabbit.—Six rabbits weighing approximately 2 Kg. each received 1 cc. per second of solution of m-hydroxyprocaine until respiratory collapse ensued. This was followed shortly thereafter by cardiac stoppage. The minimum lethal dose averaged 72 mg. per kilogram (low 62 and high 95). In 3 rabbits, using procaine hydrochloride, the average minimum lethal dose was 44 mg. per kilogram. The value for procaine hydrochloride in the literature averages 55 mg. (4).

Intraperitoneal Injection in Rat. The LD_{50} of m-hydroxyprocaine for the rat after twelve hours was determined by intraperitoneal injection. Thirty animals were employed. The LD_{50} was found to be approximately 240 mg. per kilogram. Our value for procaine hydrochloride is 184 mg. per kilogram. Our data on the toxicity for procaine hydrochloride agree well with those of Rose et al. (5). In comparing the deaths produced by each substance, however, it was observed that most of the convulsions and deaths produced by procaine hydrochloride occurred within five to six minutes and those produced by m-hydroxyprocaine occurred within the first hour of the observation period.

Intraperitoneal Injection in Mouse.—The LD_{50} of m-hydroxyprocaine for the mouse after twelve hours was determined by intraperitoneal injection. Seventy-six animals were used. The LD_{50} was found to be approximately 220 mg. per kilogram for m-hydroxyprocaine; that for procaine hydrochloride was 180 mg. per kilogram.

Intravenous Injection in Dog.—The use of procaine hydrochloride intravenously in the treatment of arthralgias is becoming increasingly

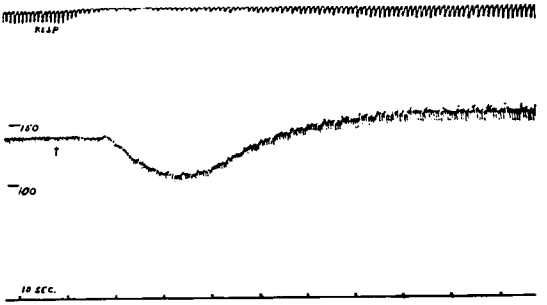

FIG. 1. Effect of intravenous administration of 1 cc. of 2 per cent procaine hydrochloride solution. Dog weighed 5 Kg.; ether anesthesia was employed.

important. Schamp (6) studied intravenous injection of this agent in the dog. We decided to compare the effects of procaine hydrochloride and m-hydroxyprocaine injected intravenously into the etherized dog. Four dogs were used for m-hydroxyprocaine and 2 for procaine hydrochloride.

Schamp observed that the acute toxicity following intravenous administration of procaine hydrochloride in the dog varied directly with the speed of administration. This was obtained also with m-hydroxyprocaine.

Two dogs weighing approximately 5 Kg. each received, intravenously, 1 cc. each of 2 per cent procaine hydrochloride and 2 per cent m-hydroxyprocaine, respectively. Figures 1 and 2 show the effects of the two compounds on the arterial pressure and respiration. Electrocardiograms observed on dogs during and after the injection of 1 cc. of

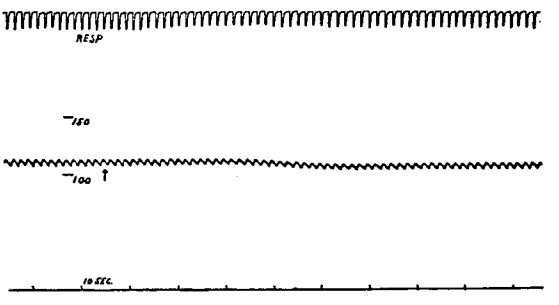

FIG. 2. Effect of 1 cc. of 2 per cent m-hydroxyprocaine sodium salt solution given intravenously. Same dog as shown in figure 1.

m-hydroxyprocaine were essentially normal. A slightly accentuated downward displacement of the S segment was present in lead II. This was a constant finding and increased with increasing dosage.

In each of these experiments the animals were ultimately killed by the injection of lethal doses of procaine hydrochloride and m-hydroxyprocaine, respectively. The terminal syndrome of respiratory failure followed by cardiac depression and a precipitous fall in blood pressure was characteristic of each compound. The lethal doses were of the same order of magnitude.

COMMENT

Bignon (7) (1892) appears to be the first individual to observe that alkalinization increased the potency of local anesthetic agents. He employed an alkalinized cocaine suspension, so-called "cocaine milk." Gros (8), in 1910, found that the free base of procaine was six times as potent as the hydrochloride in intradermal wheal tests in man. Gerlough (9) observed that the duration of anesthesia varied directly with the hydroxyl ion concentration of the local anesthetic solution. He found that procaine base pH 8.32 exhibited the anesthetic potency of a molecular equivalent of butyn, or 1 Gm. of procaine base was the equivalent of 1.7 Gm. of butyn.

Our studies show that the "orthoform type" of procaine molecule provides an excellent chemical means of producing a clinically available alkaline procaine type of local anesthetic. The potency of m-hydroxyprocaine was found to be superior to that of procaine hydrochloride on the frog's foot, rabbit's cornea and the guinea pig's sciatic nerve. By intradermal testing in man the activities appeared to be comparable. The toxicity of m-hydroxyprocaine is significantly less than that of procaine hydrochloride when injected intravenously in the rabbit. Vasomotor and respiratory responses in the dog were found to be less pronounced with m-hydroxyprocaine that with procaine hydrochloride on intravenous injection. Studies of acute toxicity on intraperitoneal injection in the rat and mouse after twelve hours showed no significant difference in toxicity. The terminal syndromes were similar. Convulsions and death, however, occurred much more promptly with procaine hydrochloride than with m-hydroxyprocaine.

M-hydroxyprocaine produced a typical spinal anesthetic syndrome upon intrathecal injection in the dog.

CONCLUSIONS AND SUMMARY

M-hydroxyprocaine has been prepared and its sodium salt studied pharmacologically. The sodium salt of m-hydroxyprocaine appears to be generally more potent and less toxic than procaine hydrochloride. These studies with m-hydroxyprocaine sodium salt suggests its availability as a local anesthetic agent for clinical trial.

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SECOND BIENNIAL WESTERN REGIONAL CONFERENCE ON ANESTHESIA

"Circulation" will be the theme for the Second Biennial Regional Conference on Anesthesia to be held at the Hotel Coronado, San Diego, on April 2–4, 1951. Many leading anesthesiologists and specialists in related fields are scheduled for program participation. The program will be presented immediately preceding and at the same place as the oral examination of the American Board of Anesthesiology.