THE PHARMACOLOGIC ACTIONS OF INTRAVENOUS PROCAINE AS AN ANALGESIC AGENT *

ROBERT M. ISENBERGER, M.D.†
Kansas City, Kansas

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THERE is an increasing interest in the potential analgesic value of procaine hydrochloride when administered by intravenous injection. This procedure is relatively new and requires precision in its use. Although the basic pharmacology of local anesthetic agents is well known, in order to appraise the current opinions on the subject, it seems appropriate at this time to review the systemic effects of intravenous procaine.

The use of local anesthetics dates back to 1884, when Karl Koller introduced cocaine into medical practice. In the course of a few years it became apparent that injected cocaine was absorbed, often with toxic reactions. Some observers believed that the drug produced a variable degree of general analgesia, and this possibility was tested by Kast and Meltzer (1) in 1906. They injected cocaine solution into the abdominal wall and muscles of experimental animals by the Schleich method of infiltration. Following these injections, the dogs developed what was described as anesthesia of both the normal and inflamed viscera of the abdominal cavity.

In 1905 Einhorn succeeded in synthesizing procaine as a substitute for cocaine. Studies by Eggleston and Hatcher (2) demonstrated the relative safety and rapid destruction of procaine following intravenous injection in dilute solution. It remained for Lundy (3) to apply the intravenous administration of procaine clinically in 1940 for the relief of the pruritus of jaundice, and for Gordon (4) in 1943 to extend the use of this procedure to the relief of pain associated with burns. Since that time many investigators have made additional contributions to the knowledge of analgesia by the use of intravenous procaine hydrochloride.

First, it is important to recall the special affinity of procaine, and other nerve depressants, for the sensory components of nerve fibers. Procaine base is liberated in the slightly alkaline body fluids, and in this form is lipoid soluble. By reversible combination with nerve

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† From the Department of Pharmacology, University of Kansas School of Medicine, Kansas City, Kansas.

protoplasm the procaine first attacks the sensory fibers because they are smaller, thereby exposing the largest surface area per unit of volume, and because they have a thinner myelin sheath. In this manner, differential penetration of procaine in proper concentration may completely block sensation before abolishing transmission of motor impulses. Since this effect is strictly local, the anesthetic must usually be applied in such a way that an effective concentration reaches the nerve supply of the part which it is desired to affect.

It is also necessary to consider the speed with which many local anesthetics are metabolized in the body. All of them are disposed of largely by the liver, but at different rates, and this rate of destruction is the deciding factor in the safety of each anesthetic agent. Procaine, as an example, is rapidly hydrolyzed, and its toxicity is relatively low. After rapid intravenous administration, however, quick hydrolysis may not be adequate to prevent accumulation of dangerous levels of procaine in the blood and vital tissues. Procaine also diffuses rapidly and in this way tends to develop toxic concentrations. Such symptoms as restlessness, apprehension, tremors, confusion, delirium, and convulsions may develop in quick succession. This early phase of stimulation may be absent or transitory, and may be replaced or followed by sudden failure of the circulation and respiration.

Obviously procaine should be used in the lowest effective concentration and in the least total amount compatible with the purpose for which it is intended, and treatment of reactions must be adjusted to the needs of the individual patient.

MECHANISM OF ANALGESIC ACTION OF PROCAINE

Several possible explanations for the analgesic effect of intravenous procaine have been suggested by State and Wangensteen (6).

1. Potentiation of the normally secreted epinephrine content of the body.
2. Direct action of procaine on the arterioles and capillaries with widespread vasodilatation.
3. Antihistamine action.
4. Anti-acetylcholine action.
5. Direct action on the nerve fibers carrying pain impulses from the affected parts.

The work of Dreisbach and Nai Chu (7) contradicts the antihistamine theory. They showed that procaine injections failed to protect guinea pigs against histamine toxicity, and against such allergic reactions as anaphylactic shock produced by the injection of horse serum in sensitized animals. Harvey's experiments (8) identified some of the actions of procaine with the effect of curare. Procaine, like curare, depressed the response of the terminal efferent nerve fibers to acetylcholine. It also diminished the response of the sympathetic ganglionic

synapses to acetylcholine, and lessened production of acetylcholine at these sites. In serum sickness the spreading flare around the wheal may be the result of liberation of acetylcholine at the nerve endings in the terminal arterioles, and disappearance of this flare after injection of procaine might be explained by anti-acetylcholine action. There is some evidence that conduction in nerve fibers depends upon release and removal of acetylcholine, associated with changes in the surface membrane and a flow of current with the propagation of an impulse. This process may be inhibited by the neutralizing effect of procaine on acetylcholine. More directly, the procaine may penetrate nerve tissue because of lipoid solubility, decrease oxygen consumption, and interfere with the oxidative metabolism of the nerve cell (9).

Local anesthetic agents, if suitably applied to peripheral sensory nerves, abolish not only the sensation of pain but other special sensations. Heinbecker (10) has shown that in the skin they paralyze first the vasoconstrictor reaction, then progressively the sensations of cold, warmth, touch, tickling, pressure, pain, and "joint sense." Here again we see a predilection of nerve depressants for certain modalities of sensation.

Bigelow and Harrison (11) measured the cutaneous pain threshold under various conditions in 5 subjects according to the technic of Hardy, Wolff and Goodell, which uses radiant heat as the source of painful stimulation. The subjects were carefully instructed as to the end point, namely the first appearance of a pricking pain. Pain threshold determinations were made on the forehead. The procaine solution was injected subcutaneously in the arm. A 2 per cent concentration was employed in doses ranging from 5 to 40 cc., that is 100 to 800 mg. They concluded that procaine has a general analgesic effect in addition to its well-known local anesthetic properties. The maximum rise in the cutaneous pain threshold attributable to the general action of this drug was about equal to that after administration of acetylsalicylic acid, that is, 35 per cent of the normal threshold value. The duration of the procaine effect was much shorter than that of the acetylsalicylic acid. The general analgesic effect of procaine was usually more pronounced when other central effects of the drug, such as giddiness, were also evident.

Inasmuch as procaine is rapidly hydrolyzed, and unless it is established that one of the metabolites is the active agent, one should attempt to explain the accumulation of sufficient procaine after intravenous administration for analgesia in the affected areas of the body. Perhaps the answer lies in the theory that regions of injury, inflammation, edema, and pain suffer increased capillary permeability, with sufficient diffusion of procaine into the tissues for localized anesthesia of the nerve endings. On this basis, Allen (12) has expressed doubt of adequate duplication of the recent clinical uses of procaine on a physiologic basis in animals, and he believes that the "new concept" of

certain pathologic processes may be still more difficult to elucidate in the laboratory.

METABOLISM OF PROCAINE

In 1942, Legge and Durie (13) showed that procaine added to whole blood was rapidly converted to para-aminobenzoic acid, and recently Forney, Hulpieu, and Cole (14) have made quantitative estimations of the amounts of procaine and of p-aminobenzoic acid in the blood and other tissues of the dog following intravenous procaine. With an injection rate of 1.5 to 2.5 mg. per kilogram per minute, a maximum blood concentration of procaine of about 4 mg. per cent was reached. The p-aminobenzoic acid measured 30 mg. per cent when death of the animals occurred.

In human blood, procaine is hydrolyzed by an esterase, and some of the acid formed is then acetylated by the liver. Lief, Poet, and Brodie (15) gave procaine hydrochloride intravenously to different human subjects and measured the levels of procaine, p-aminobenzoic acid, and of diethylaminoethanol in the urine and plasma. Urine excretion accounted for only 1 per cent, para-aminobenzoic acid for 75 per cent, and diethylaminoethanol for about 25 per cent of the administered procaine. Procaine disappeared rapidly from the plasma, and only traces were found, even during injection. Appreciable concentration of diethylaminoethanol persisted in the blood, and this derivative was therefore suggested as the active agent. It has been found to be much less toxic than procaine, and may be administered orally in relatively large doses. Blood plasma appears to contain an enzyme or procaine esterase, probably formed in the liver, which is capable of destroying procaine. This enzyme can be inhibited by administration of neostigmine, after which procaine toxicity is increased in mice, rats, and dogs. This was demonstrated by Conway, Ting, and Coon (16) in 1948. They observed that after neostigmine, intravenous procaine produced death almost instantaneously, without any preliminary phase of convulsions. In view of these results, simultaneous administration of procaine and neostigmine would appear to involve some additional hazard.

The rapid hydrolytic destruction of procaine by the liver and by procaine esterase is doubtless an important factor in present-day therapy with this drug. It would seem to play a part, for example, in Burstein's observations (17), that intravenous procaine involves the risk of toxic effects if given in amounts adequate to prevent cardiac arrhythmias of cyclopropane anesthesia, whereas treatment of this disturbance by procaine injections is a safe and effective procedure.

TOXIC EFFECTS OF INTRAVENOUS PROCAINE

Toxic reactions to intravenous procaine depend on the total dose administered, the speed of the injection, and the concentration of the

solution used. Adams (18) has stated, and it is a common laboratory observation, that in dogs small amounts cause a slow rise in blood pressure and stimulation of respiration, which may terminate in convulsions. Larger amounts produce an abrupt fall in blood pressure from vasodilatation and cardiac depression, together with respiratory paralysis of central origin. If large amounts are given rapidly the result may be sudden respiratory standstill and cardiac arrest, with death of the animal. When a slower rate of injection is used, it has been estimated that a fatal dose of procaine can be destroyed by the cat every twenty minutes.

For the relief of muscle spasm of acute and subacute poliomyelitis, Mitchell, Terry, and Faggard (19) gave procaine intravenously in 500 cc. of salt solution at the rate of 10 to 40 mg. per minute per patient for a total dose of from 1 to 4 Gm. A few of the patients complained of slight dizziness, tingling of the lower extremities, and of seeing spots while receiving the drug. Some rise in pulse rate with a small drop in systolic pressure was noted. In no instance did they find it necessary to reduce the rate of injection. In the use of procaine by vein for analgesia in burns, urticaria, arthralgia, and so forth, other investigators have reported dilated pupils, apprehension, tremors and unconsciousness (20). Allen (21) recorded occasional convulsions, relieved by barbiturates, following the use of procaine for analgesia in the second stage of labor.

In our study of procaine toxicity at the Mayo Clinic (22) collapse reactions were observed in several patients given sacral injections of 60 to 100 cc. of 1 per cent procaine for rectal anesthesia. No preliminary phase of stimulation occurred, except for occasional apprehension and mental confusion. The chief disturbance was a fall in blood pressure, usually a slow pulse, shallow respiration, pallor of the skin, cyanosis of the mucous membranes, sweating, nausea, and sometimes vomiting. These reactions were greatly reduced following preliminary medication with barbiturates and small doses of morphine. When we attempted to reproduce these clinical effects in the laboratory, it was observed that soluble barbiturates prevented excitement and convulsions, but failed to protect against fatal respiratory and circulatory depression of large intravenous doses of procaine. Some dogs died because of too rapid administration of an excessive amount of sodium amytal for the relief of procaine convulsions. These results conform with the opinion that soluble barbiturates should be given slowly to patients who develop procaine convulsions and in amounts sufficient only to prevent spasmodic interference with the respiratory excursions of the chest wall and diaphragm. We also produced respiratory paralysis in dogs by the intracisternal injection of 60 mg. of procaine hydrochloride (23). The paralysis lasted for approximately one hour. When the animals were given 30 mg. of ephedrine sulfate simultaneously with the procaine, intracesternally, the duration of respiratory

paralysis was reduced to an average of twenty minutes, and in some animals it was completely abolished. We felt justified in concluding that ephedrine and procaine were directly antagonistic in their effects on the respiratory center of the medulla.

It is apparent that animals and man show similar toxic reactions to procaine in certain circumstances, and that barbiturates, ephedrine, oxygen, and even artificial respiration may be indicated as treatment, with special emphasis on the need for their prompt availability and cautious administration.

INTRAVENOUS PROCAINE IN COMBINATION WITH GENERAL ANESTHETICS

Hulpieu and Cole (24) have made some valuable studies of procaine metabolism during light anesthesia. They gave procaine hydrochloride intravenously at various constant rates to dogs under plane 1 anesthesia. Dogs under pentothal withstood considerably larger doses and lived longer than those under chloroform. Dogs under chloroform were more resistant than those under ether. At death the blood levels of procaine were approximately the same under pentothal as under chloroform, but under ether they were about 60 per cent lower. Conversion of procaine to p-aminobenzoic acid was most rapid under pentothal and slowest under ether. These results suggest reduced tolerance to intravenous procaine under light ether when compared to procaine tolerance during pentothal anesthesia.

Kraft (25) reported that intravenous procaine may be used to reduce the amount of gaseous anesthetic agents, the dosage of spinal anesthetics, and the requirements for intravenous pentothal especially in patients who are poor surgical risks.

RESULTS

Although animal studies are often unsatisfactory substitutes for accurate clinical observation, our results on dogs do not encourage the belief that intravenous procaine, in safe dosage, has any appreciable anesthetic properties.

In a small series of seven preliminary experiments we have attempted to "buffer" the stimulating effects of procaine with simultaneous administration of pentothal, curare, and pentothal-curare mixtures. By these combinations we hoped to fortify the latent procaine analgesia, and to establish a more potent anesthetic effect in which undesirable reactions were mutually antagonized. At the present time we have been unable to demonstrate manifest analgesia from intravenous procaine in dogs, in doses as large as 1 mg. per kilogram per minute for a period of one hour. This is a usually fatal dose of 60 mg. per kilogram. Procaine hydrochloride alone by vein produced rapid pulse, excitement and mild convulsions without demonstrable analgesia.

When the excitement, tremors, and convulsions were prevented by simultaneous, protective doses of intravenous pentothal and curare, intravenous procaine, to the limit of tolerance, failed to intensify the pentothal and curare analgesia. Rapid pulse and marked fall in blood pressure occurred.

The net result of intravenous procaine appeared to be a reduction of the analgesic, hypnotic, and relaxing action of pentothal and curare.

SUMMARY

Intravenous procaine produces moderate analgesia, relief of pruritus, and increased peripheral circulation in a variety of clinical conditions.

The action appears to be localized to the nerve and blood supply of the affected parts.

Procaine undergoes prompt hydrolysis with rapid disappearance from the blood stream, requiring intravenous infusion in low concentrations. There is some evidence that the metabolites, para-aminobenzoic acid and diethylaminoethanol, retain some of the activity of the injected procaine.

Toxic reactions to intravenous procaine depend on the total dose administered, the speed of injection, and the concentration of the solution used. Individual idiosyncrasy is not uncommon.

In the normal dog, pain perception is not appreciably depressed by maximum tolerated doses of procaine intravenously.

The analgesic, hypnotic, and relaxing action of intravenous pentothal and curare in the dog is reduced by the simultaneous injection of procaine.

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The Annual Meeting of the Massachusetts Medical Society will be held on May 24, 25, and 26, 1949, in the Worcester Memorial Auditorium, Worcester, Mass.

The Section on Anesthesiology of the Massachusetts Medical Society will meet in the Worcester Memorial Auditorium on Thursday, May 26, 1949, between the hours of 12:00 noon and 2:00 p.m. This will be a luncheon meeting, and Dr. Robert D. Dripps, Head of the Department of Anesthesiology at the University of Pennsylvania, will discuss, "A New Plan for Graduate Teaching of Anesthesiology."

On Thursday, May 26, 1949, at 2:25 p.m. Dr. Dripps will also speak on the General Session of the Massachusetts Medical Society, and his topic will be, "Pitfalls in Anesthesiology."