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CURRENT COMMENT

A RESUME OF INTRAVENOUS PROCAINE THERAPY*

FRED B. MOOR, M.D.

The most surprising development among new uses for old drugs is the intravenous injection of procaine for a variety of clinical conditions. This drug was synthesized by Einhorn in 1905. In 1909 Bier produced anesthesia in the extremities by injecting procaine intravenously distal to a tourniquet. On account of the occasional fatal outcome from the use of procaine for local anesthesia, however, it has, until recently, been considered unsafe to inject the drug into the venous circulation. Now that it has been shown that procaine can, with comparative safety, be administered intravenously, its clinical use is expanding rapidly.

CHEMISTRY AND PHARMACOLOGY

Procaine hydrochloride is para-aminobenzyl-diehylaminoethanol hydrochloride:

\[
\text{H}_2\text{N} - \text{C}_6\text{H}_4 - \text{C}=\text{C} - \text{C}_2\text{H}_5 - \text{CO} - \text{O} - \text{CH}_2 - \text{CH} - N\{(\text{C}_2\text{H}_5)_2\} - \text{HCL}
\]

Procaine hydrochloride occurs as colorless crystals which are soluble in 0.6 part of water and 30 parts of alcohol. It is stable to temperatures as high as 100 C.

Goldberg, Koster, and Warsaw have shown that when procaine is injected, it is hydrolyzed in the liver by an esterase into para-aminobenzoic acid and diethylaminoethanol. The para-aminobenzoic acid is then acetylated. In 1919, Eggleston and Hatcher demonstrated that nearly 95 per cent of injected procaine may be recovered in ten to twelve hours from the urine as para-aminobenzoic acid, paraaminohippuric acid, para-aminobenzoyl glucuronate, diethylaminoethanol, and traces of procaine. Graubard et al. found that twenty minutes after the intravenous injection of 20 mg. of procaine per kilogram of body weight in the rabbit, only traces could be found in the blood stream of the animal. On the basis of this study these authors evolved a dosage method based on body weight for the human as follows:

\[4 \text{ mg/kilogram of body weight} = 1 \text{ procaine unit in 20 minutes.}\]

It was recommended that this be given in a 0.1 per cent solution, so that 1 mil contained 1 mg. of the drug. From clinical experience, the authors found this dosage to give optimal results with a minimum of toxic reactions.

Mautz showed that the local application of procaine to the heart reduced the irritability of the myocardium so that a considerably stronger stimulus was needed to produce ventricular fibrillation. Burstein et al. demonstrated that ventricular fibrillation could be produced in the experimental animal by the intravenous injection of epinephrine during cyclopropane anesthesia. It was possible to prevent the occurrence of fibrillation, if the injection of epinephrine was preceded by an intravenous injection of procaine.

One of the surprising effects of the intravenous administration of procaine is the clearing up of urticarial skin manifestations in serum sickness and other allergic conditions.

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Graubard et al. believe that Procaine has a twofold action in traumatized and inflamed tissues: (1) direct action on irritated nerve fibers; (2) indirect action of diethylaminoethanol on the endothelium of blood vessels and capillary walls to lessen fluid loss from the blood to the tissues. The latter idea is based on the structural similarity of diethylaminoethanol to Benadryl which has well-known antihistamine activity. Most investigators agree that Procaine is concentrated in traumatized or inflamed tissues because of the exudation which occurs there.

The concentration employed and the administration of Procaine has varied considerably with different investigators and with purposes for which the drug has been given. This will become apparent when the clinical application of intravenously administered Procaine is discussed.

The subjective manifestations of intravenous Procaine injection in the conscious patient are usually not unpleasant. In five to seven minutes after the injection is started there is a sensation of warmth over the entire body. There is comfortable relaxation as pain is relieved. There is some dryness of the mouth and a metallic taste. There is likely to be transient lightheadedness. The operator may observe flushing of the face and neck, tearing of the eyes, and dilatation of the pupils. More severe responses are marked dizziness, apprehension, sensation of trembling, sleepiness beyond comfortable relaxation, and momentary loss of consciousness.

TOXICOLOGY

The minimal lethal dose of Procaine hydrochloride for the rabbit is 40 to 60 mg. per kilogram of body weight, 40 to 45 mg. per kilogram for the guinea pig, and 45 to 75 mg. per kilogram for the dog. The minimal lethal dose for man is unknown. It has been suggested that many of the deaths attributed to Procaine during local anesthesia may have been due to its combination with epinephrine rather than to the Procaine alone, since epinephrine increases the toxicity of Procaine about threefold. With the too rapid intravenous injection of the 1 per cent solution of Procaine hydrochloride convulsions may occasionally occur, but these are controlled by stopping the flow or by the intravenous injection of a barbiturate.

Since the burden of the destruction of Procaine in the body falls upon the liver, one might expect evidence of damage to this organ. Jacoby et al., however, have recently demonstrated that repeated massive doses of Procaine hydrochloride administered to rats and dogs in acute and subacute experiments produce no histologic evidence of damage in the liver, the spleen, the heart, or the kidney. Liver function tests done on human beings after the administration of Procaine intravenously gave no indication of impaired hepatic function. Richards has shown that starvation and a deficiency of Vitamin C markedly increase the toxicity of Procaine. He postulated that Vitamin C may be part of an enzyme system concerned with the destruction of Procaine. He suggested the administration of large doses of Vitamin C and glucose before the use of Procaine in poorly nourished patients.

A few, but by no means all, of the investigators who have done the pioneer work on the intravenous use of Procaine recommend a preliminary skin test to determine the sensitivity of the patient to the drug. It is suggested that 1 cc. of the 0.1 per cent solution be injected intradermally. If the patient is sensitive, the reaction is apparent in about ten minutes. Another wise precaution is the preliminary administration of a therapeutic dose of a barbiturate. When Procaine is to be injected intravenously, an injectable barbiturate should be available for immediate intravenous administration.
Procaine has been used successfully by the intravenous route for the relief of various pruritic conditions. Lundy, in 1940, used 20 cc. of 0.1 per cent procaine intravenously for the treatment of pruritis in jaundiced patients. State and Wangensteen encountered delayed serum sickness following the injection of crystallized bovine albumin as a blood substitute. In order to relieve the severe joint pain which their patients suffered, they gave 1 gm. of procaine hydrochloride in 500 cc. of physiological saline solution during a period of two hours. To their surprise, all the manifestations of serum sickness subsided almost immediately. Appelbaum et al. observed rapid disappearance of the urticarial rash and the joint symptoms of serum sickness, resulting from a prophylactic dose of tetanus antitoxin, following the intravenous injection of 1 gm. of procaine hydrochloride in 500 cc. of physiological saline solution. Dressler and Dwork have reported the almost immediate subsidence of the arthralgia and the urticarial rash produced by penicillin in a sensitive patient. Their dosage of procaine was 1 gm. in 500 cc. of physiological saline by the intravenous route.

Graubard et al. employed a 0.1 per cent solution of procaine hydrochloride in a dosage of 4 mg. per kilogram of body weight with gratifying results in the treatment of traumatic conditions. This dosage should not be administered in less than twenty minutes. Among the conditions successfully treated were sprains, fractures, and traumatic arthritis.

The intravenous injection of procaine has proved to be of definite value for the prevention of cardiac irritability during thoracic surgery. Mautz, as mentioned previously, in 1936 called attention to the reduction in cardiac irritability produced by the epicardial and intravenous administration of procaine.

Burstein, and Burstein and Alexander, later reported the intravenous use of procaine hydrochloride in a large number of patients with acute cardiac arrhythmias during intrathoracic surgery. The drug was given in dosages ranging from 30 to 70 mg. in 1 per cent solution injected rapidly by vein with uniformly good results.

Bittrich and Powers have recently reported their experience in 17 cases with intravenous procaine in thoracic surgery. They employed a continuous intravenous drip of 1 per cent procaine hydrochloride at the rate of 65 to 100 drops per minute during the operative procedure. In spite of the procaine, 5 of the 17 patients developed cardiac arrhythmias. It was the authors' impression that their patients tolerated thoracic surgery better and made easier recoveries with the use of intravenous procaine.

Graubard et al. reported the intravenous injection of procaine hydrochloride in a dosage of 4 mg. per kilogram of body weight in 0.1 per cent solution in the treatment of osteoarthritis. The results were exceedingly good with the relief of pain with increased mobility for prolonged periods of time.

Gordon found the use of intravenously administered procaine of great value for the control of pain in 10 patients during the dressing of severe burns. He gave a liter of 0.1 per cent solution of procaine hydrochloride over a period of one and a half hours. Pain was relieved without the simultaneous use of morphine.

McLachlin found the intravenous use of procaine hydrochloride superior to morphine for the control of postoperative pain. In a series of ten cases he injected 1.0 gm. of procaine hydrochloride in 500 cc. of physiological saline solution in one to one and a half hours. Pain was relieved without the simultaneous use of morphine.

Allen, and Crossman et al. have actually performed major surgical procedures using a continuous
intravenous infusion of 1 per cent procaine hydrochloride given at rates up to 20 cc. per minute. They did not, however, recommend this method for general use.

Allen * in 1945 reported the use of intravenous procaine for the production of analgesia in 12 obstetrical cases at the City Hospital, Welfare Island, New York. For this purpose, a 1 per cent solution of procaine hydrochloride was given at the rate of 0.5 to 13 cc. per minute depending upon the degree of analgesia or anesthesia required.

Johnson and Gilbert, also of the City Hospital, Welfare Island, reported 20 obstetrical cases in which 1 per cent procaine hydrochloride was used intravenously as the analgesic and anesthetic agent. The only complication occurring in the 32 cases covered in these two reports was the occurrence of mild convulsions, which were easily controlled and apparently harmless. The authors, although they admitted that their series was small, believed that the method was simple and safe for both mother and child.

SUMMARY

1. The intravenous injection of procaine hydrochloride for a variety of clinical conditions constitutes a surprising new chapter in therapeutics.

2. With adequate precautions as to dosage and rate of administration, procaine can be safely given by the intravenous route in concentrations of 0.1 to 1 per cent.

3. It has been used successfully for serum sickness, the pruritis of jaundice, trauma of soft tissues, bones and joints, in the prevention and treatment of cardiac arrhythmias during intrathoracic surgery, for the relief of pain in osteoarthritis, for the control of pain during the dressing of burns, for postoperative pain, and for obstetrical analgesia and anesthesia.

4. Procaine hydrochloride should be handled carefully so that this useful new method may not be discredited by accidents and unnecessary danger to patients.

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**INTRAVENTOUS PROCAINE DURING THORACIC SURGERY**

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With increasing boldness and skill surgeons are probing into hitherto inaccessible areas, altering and remodeling tissues of some of our most vital organs and effecting surgical cures for conditions which a decade ago were accepted as unfortunate but incurable maladies. Among the most recent beneficiaries of such surgical intrepidity are those successfully undergoing surgery of the heart and great vessels. As a result of such surgery many children, once in hopeless invalidism because of some congenital cardiovascular defect, now lead normal lives, with a greatly extended life expectancy.

Surgery on the heart and paracardial structures or traction on the hilus of the lung may initiate serious arrhythmias which can result in death if not promptly controlled. Procedures involving the pericardium are particularly apt to be followed by severe derangements of rhythm. Thus anesthesiology is faced with another challenge.

Various investigators, Mautz (1936), Shen and Simon (1938), and Burstein and Marangoni (1940), have shown that irritability of the myocardium and conduction system of the heart may be reduced by topical application or intravascular injection of procaine, thus preventing fibrillations which would ordinarily occur under the conditions of the experiment. In many instances procaine re-established a normal rhythm even after fibrillation had been induced.

The recent war produced a large number of cases in which operative procedures were carried out on the heart. These provided an excellent clinical test of the above mentioned principles. Burstein reports 14 cases in which dysrhythmias were corrected during surgery by intravenous injection of 1 per cent procaine. These occurred in a series of 121 operations in which shell fragments or other foreign bodies were removed from the pericardium, myocardium, or from within or in close relation to the great vessels.

Disturbances of rhythm and shifting of the pacemaker may result either from direct stimulation of cardiac muscle or reflexly through the well-known vago-vagal mechanism. In the laboratory, cardiac arrhythmias can be produced almost at will in animals under cyclopropane anesthesia by injections of epinephrine in doses which are no more than double the amount which may be expected to be secreted during an average emotional strain. Vago-vagal reflexes may be initiated by stimulation of the pericardium or by traction on the hilus. These impulses which