1951

Intravenous procaine : its toxic effects

Robert G. Mitcheltree
University of Nebraska Medical Center

INTRAVENOUS PROCAINE; ITS TOXIC EFFECTS

ROBERT G. MITCHELTREE

Submitted in Partial Fulfillment for the Degree of Doctor of Medicine

College of Medicine, University of Nebraska

January 15, 1951

Omaha, Nebraska

INTRAVENOUS PROCAINE; ITS TOXIC EFFECTS

INTRODUCTION

During the past several years the use of procaine intravenously has gained increasing popularity in a number of clinical fields. Much has been written concerning its various uses, but few reports have dealt solely with the undesireable effects of the drug. It is, therefore, the purpose of this paper to give to the physician a concise review of the known toxic effects of intravenous procaine, as well as a brief summary of its history, pharmacology, and uses.

EARLY HISTORY

Although the widespread use of intravenous procaine has been confined largely to the past decade, its introduction into medical therapeutics was made in the early years of this century. Einhorn prepared the simple esters of para-aminobenzoic acid and later made others which formed water soluble salts (25). He introduced procaine in 1905. The first trial of the drug intravenously was by Bier in 1909, who injected procaine below the tourniquet for anesthesia during an amputation (7). Hatcher and Eggleston experimenting with dogs reported in 1916 a fall in blood pressure, respiratory arrest, decreased pulse rate, and generalized convulsions after

Administration of intravenous procaine (25). Such experimental results apparently discouraged the use of the drug by the intravenous route until 1935, when Barany reported its success for temporary relief of tinnitus aurium (7). There then followed more papers such as those of Leriche who in 1938 and 1939 used intravenous procaine for various inflamitory diseases and dystrophied states. In 1940 Lundy suggested its use for relief of puritis with jaundice, and Burstein used procaine intravenously for control of ventricular fibrillation and other cardiac arrhythmias induced by ephedrine during cyclopropane anesthesia (3). The following year Gordon advocated the drug for relief of pain in severe burns. Further detailed history of intravenous procaine will be presented in the following pages.

MODE OF ACTION

An understanding of the mechanism of procaine reaction will be found to be helpful during clinical use and observation of toxic effects. Since the relief of pain is often an indication for use of intravenous procaine, Gordon (1950) suggests that its mechanism is threefold: local anesthetic action of procaine dialized into the area of capillary permiability produced by

injury, effect on cerebral cortex or thalamus, and suppression of the local painful reaction of vasodilation and edema (a partial block of the sympathetic system).

After injection procaine is rapidly hydrolized by esterases present in the blood, liver, and body tissues into its two component parts, para-aminobenzoic acid and diethylamino ethanol (6,23). The amount of procaine remaining in the body after intravenous injection varies inversely with the elapsed time and directly with the rate of injection (6). Doak (1949) therefore assumes that when one gram of procaine hydrochloride is administered intravenously by slow drip there is never more than a small fraction of this amount of the drug existing as such in a person's body. To give an idea of the rapidity which detoxifying mechanisms react Mushin (1949) states that the therapeutic dose of intravenous procaine is completely eliminated from the body in twenty minutes. Because of the relatively rapid removal of procaine itself from the human organism its products of hydrolysis might next be briefly examined.

State and Wangensteen (1946) pointed out that the formulas for benadryl, pyribenzamine, and procaine are closely related structurally. All three drugs contain either an aminoethyl or ethylenediamine group. Both

pyribenzamine and benadryl counteract the spasmotic effect of acetylcholine and all three drugs relieve phases of serum sickness. Thus there has been suggested an antihistamine effect of procaine (23). Neither hydrolysis product effects the heart as powerfully as procaine itself (6).

The mechanism of cardiac effects is well outlined by Rittrich and Powers (1948) and others:

a. Suppression of extracardiac nervous stimulation by depression of the extrinsic cardiac nerves.
b. Suppression of adrenal medullary secretion preventing reflex liberation of ephedrine (7); and an ephedrine-potentiating action (23).
c. Decreased conduction through the bundle of His and ventricular musculature (26, 13).
d. Decreased excitability of the myocardium to electrical stimulation.
e. Increase in the refractory period after systoli.
f. Return of displaced pacemaker to a normal sinus node rhythm (3).

The peripheral vascular effects can be partially explained by the relief of reflex vasoconstriction caused by pain in the area of injury as well as in other vascular areas (8), and increasing blood supply to the

area (3).

USES

Because of its actions on nervous tissue and antihistamine-like effects, intravenous procaine has had a wide variety of clinical applications. The anesthetic properties have been utilized for such conditions as: postoperative pain (9,15), obstetrical anesthesia (1), an adjunct to spinal and pentothol anesthesias (4, 12), puritis of jaundice (24), burns (9,12), and an aid in traumatic surgery (7). In the cardiovascular field its uses include that of : cardiac surgery (9,16), postoperative embolism (9, 24), ventricular fibrillation (24), the shoulder-hand syndrome (14), thrombophlebitis, coronary disease, and Buerger's disease (16). Both Schrum and Mushin (1949) report the usefullness of intravenous procaine for severe allergic conditions, and Boyer (1950) has employed it for cases of delayed penicillin reaction. The collegenous tissue diseases,acute rheumatic fever, glomerulonephritis, periarteritis nodosa and lupus erythematosis, have all been treated with procaine intravenously (10). Its use also extends to neuromusculoskeletal disorders such as low back pain, rheumatoid arthritis, and osteoarthritis (14). Finally, Olsen (1950) describes its application for various

mental disorders.

Few reports of specific contraindications appear in the literature. Hulpieu (1950) states that severe infections, liver disease and marked obesity tend to give higher levels of procaine in the blood; while hypertension with kidney involvement produces high blood levels of para-aminobenzoic acid. In dog experiments (13,26) there is suggested a potential hazard in cases of pre-existing cardiac damage. Doak (1949), however, reports that electrocardiogram changes in the normal heart indicate that the organ is not significantly effected by the ordinary doses used.

DOSAGE

Before administration of procaine itself intravenously, a plan of premedication is helpful and can be divided into three stages. A history should first be taken concerning possible procaine sensitivity; for it must be remembered that dentists, physicians, nurses, and technicians have all had previous contact with the drug. A second safeguard against procaine sensitivity consists of an intradermal test for reaction using dilute solutions (14,20). A small dose of barbiturate given a few minutes before intravenous administration of procaine offers a third protection against a drug

reaction (13, 20, 22).

The use of a weak solution of procaine for intravenous use has become more popular in the following forms :

1. 1:1000 solution of 1000 cc. given in one hour (12, 16).
2. 4 mgm. per Kg. in 0.1% solution (16).
3. 6 mgm. per Kg. in 0.1% saline or water, given in 20 to 30 minutes (14)

Stronger solutions can be used, however, but with more caution :

1. 0.2% slowly (4).
2. 20 cc. of 0.5% solution in saline (5).
3. For emmergencies 10 cc. of 1% solution (16)

TOXICITY

"Toxic reactions of procaine hydrochloride fall into two categories, idiosyncrasy and true toxocity. True toxicity is a poisoning effect of a normally safe drug when taken in excessive dose. Idiosyncrasy is defined as an abnormal or unusual response to a drug" (Sachs, 1949). There exists a marked variation in the rate of procaine injection which can be tolerated by various individuals. When the intravenous drip is too slow, the

Therapeutic action of procaine may fail (6). It must also be remembered that the dose is ordinarily eliminated from the body in twenty minutes (16). Mushin (1949) points out that vitamin C deficiency will increase the tendancy toward toxic reactions. Marton (1949) reports the death of a sixty-nine year old white female who was given procaine intravenously for a painful neuromuscular disorder. Her electrocardiogram previously showed signs of left ventricular strain, but drug sensitivity was considered to be the cause of death. The objective and subjective effects of intravenous procaine may often be confusing and lead to a difficult differential diagnosis as illustrated in the following case:

CASE REPORT A twenty year old white female entered the hospital on 8-18-50, with the diagnosis of recurrent chronic appendicitis and vericosities of the broad ligaments. Physical examination revealed a healthy girl of 110 pounds, blood pressure 112/68, with abdominal pain and tenderness in the lower abdominal quadrants. Hemoglobin was 81%. On the following morning she was prepared for surgery with morphone gr. 1/6 and scopolamine gr. 1/150. The operation began at 9:15 A. M. using sodium pentothol, nitrous oxide and curare anesthesia. The appendix was removed and a

bilateral ovarian denervation performed. Anesthesia proceeded uneventfully, blood pressure remained at 100/60, and the patient was returned to her room at 10:40 A. M. in good condition. At 11:15 A. M. she was given 1000 cc. of 5% glucose intravenously with one gram of procaine hydrochloride added to the solution. By noon she became restless and the blood pressure dropped to 90/50. At 3:45 P. M. her pressure had fallen to 60/40 with a pulse of 104, and she developed nausea and vomiting. Abdominal tenderness was no more than could be expected after her surgery, suggesting a drug reaction rather than hemorrhage. By 7:30 P. M. her blood pressure rose slightly to 72/54 with a pulse of 120. A total of 3000 cc. of fluids and 1000 cc. of whole blood were given intravenously; so that by 11:30 P. M. blood pressure and pulse remained normal at 118/70 and 76, but hemoglobin was only 61%. Physical examination several weeks later revealed no evidence of a pelvic mass, adhesions, nor any suggestion that she had had postoperative hemorrage. The final impression was that this patient had a procaine sensitivity reaction.

It is, therefore, very important for the physician

who uses procaine intravenously to have a good working knowledge of the toxic effects of this drug so that he will differentiate procaine toxicity or procaine idiosyncrasy from such conditions as postoperative hemorrhage, shock, epileptiform seizures, and pulmonary conjestion.

The toxic effects of intravenous procaine will be classified according to the cerebral, autonomic, cardiac, and anaphylactic reactions. Mild cerebral manifestations, presented in as nearly their order of occurance as possible, begin five to seven minutes after injection as a feeling of generalized body warmth (2,8). There may or may not occur a flush over the head, neck, and face (except for a circumoral pallor)(8). The patient may next notice a dryness of the mouth with often a metalic taste (8, 14), followed by tearing of the eyes, dilation of the pupils, light headedness and dizziness (8, 20). If administration of procaine is continued, more serious toxic effects may be noted by both physician and patient. Subjectively the patient experiences quite frequently opression, drousiness, apprehension, or malaise (2, 8, 14, 16, 20). He develops a headache which may be followed by confusion, euphoria, aphasia (17), or numbness of the fingers (14, 16). While watching the patient during these reactions, the physician

may observe him progressing from fine tremors (8, 14, 16) to generalized convulsions (16,20) and finally unconciousness (8, 20).

Olsen (1949) states that widespread but transient disturbances of the nervous system are manifest by numerous symptoms. Usually reactions last less than fifteen minutes but occasionally as long as a week. Periventricular symptoms include: anxiety, rage, hallucinations, poverty or flight of ideas, nausea, vomiting, and diuresis. Tactycardia, respiratory paralysis and circulatory collapse are medullary reactions which effect chiefly the cardiovascular-pulmonary systems.

Cardiovascular changes after use of procaine are in general a result of nervous tissue response. Generalized circulatory depression and finally collapse result from depression of the cardiac center of the medulla (17, 25). Electrocardiogram changes include prolongation of the PR and QRS intervals and alterations in configurations of all complexes (26). In dog experiments Long (1949) found that small doses of procaine intravenously caused changes in the height of the R wave, T wave, and S-T segment. Increasing the dose produces, successively, bundle branch block, slowing of condition through the

A-V node, ventricular tactycardia, and, ultimately, ventricular fibrillation. As the bundle branch block increases, the force of contractions of the heart is decreased. Drops in blood pressure are, therefore, a combined result of relaxation and dilation of peripheral vessels, medullary depression, and decreased conduction through both extrinsic and intrinsic cardiac nervous elements, all of which, under normal conditions, would tend to stabilize blood pressure.

Anaphylactic reactions to intravenous procaine may be either immediate or late. Early signs may be manifest as respiratory asthma (14). Schiff (1949) reports a case in which the patient had undergone daily intravenous administration of procaine for one month followed by respiratory distress. One month later other attempts at the same therapy caused anaphylactic reaction in spite of negative intradermal tests.

TREATMENT OF TOXICITY

Not every patient will show a definite toxic response to procaine when given intravenously. Graubard (1947) with 2000 cases reports no case of procaine sensitivity nor any contraindication for use of the drug. While studying results of cephalin flocculation test after procaine, Steinberg (1949) found no evidence

of impared liver function in his six patients. Allen (1945) used intravenous procaine in twelve deliveries and observed no harm to mother or baby.

Reactions may occur, however, in any patient, and the physician should recognize and treat the toxic effects. First, the injection must be stopped immediately. True toxic symptoms are usually handled by use of oral or intravenous barbiturates (1, 15). Anaphylactic reactions require two minums of 1:1000 epinephyrine subcutaneously (15). Artificial respiration and intravenous fluids must support the patient who develops pulmonary or circulatory collapse (13).

SUMMARY

Procaine, when given intravenously, may or may not cause a toxic reaction in a specific patient. Arbitrarily I have divided these reactions into four groups.

Cerebral effects progress from mild to severe forms and theoretically become reversable upon withdrawal of the drug. The patient first notices a generalized bodily warmth, dryness of the mouth with a metalic taste (presumably of procaine), tearing of the eyes, dilation of the pupils, and dizziness. Mental states

vary from euphoria to confusion and aphasia. Fine tremors and generalized convulsions may finally lead to unconsciousness.

The autonomic response of the medulla causes tactycardia, respiratory paralysis, and circulatory collapse. Periventricular reactions from procaine can result in anxiety, rage poverty or flight of ideas, hallucinations, nausea, vomiting or diuresis.

Cardiac changes during procaine therapy include prolongations of the PR and QRS intervals, changes in configurations of all EKG complexes, changes in the height of the R wave, T wave, and S-T segments, and evidences of bundle branch block. Because of the result- and depression of the cardiac center in the medulla, suppression of intrinsic and extrinsic cardiac nerves, and peripheral vasodilation, this author wishes to raise the following question: Does intravenous procaine strip the body of its primary defenses against cardio-vascular collapse?

An anaphylactic reaction or idiosyncrasy to procaine may appear as respiratory asthma, occuring early or late.

Before giving procaine intervenously one should obtain a negative history of procaine sensitivity, inject a dilute solution of procaine intradermally to test for a reaction, and give the patient a small dose of barbiturate. The safest and most popular method of administration is the addition of one gram of procaine hydrochloride to one liter of saline (0.1% solution) given intravenously by slow drip. If a reaction develops discontinue the drug innediately and give the patient a barbiturate for true toxicity or ephedrine for an anaphylactic reaction. Remember that procaine is completely removed from the body in twenty minutes and that toxic effects are generally reversable but may rarely last as long as one week.

CONCLUSIONS

1. The therapeutic use of procaine is based on its properties of: local anesthetic action, relief of vasospasm, and nervous tissue changes.
2. Toxic reactions to intravenous procaine do occur, usually to mild degree, but may present a difficult differential diagnosis.
3. These toxic reactions effect the cerebrum, autonomic centers, and cardiovascular system. Drug sensitivity will produce an anaphylactic reaction.

4. By careful premedication and dosage of intravenous procaine its toxic manifestations can be minimized.

BIBLIOGRAPHY

1. Allen, F. M.: Intravenous Obstetrical Anesthesia, Am. J. Surg. 70:283 1945

2. Boyer, D. W., Barwick, J. T. F., And Meidt, C. E.: Use of Intravenous Procaine in a Miscellany of Cases. Rocky Mountain J. M. 1950, 47 No. 2 (Feb) 110-4

3. Broadhead, H. E.: Present Day Uses of Intravenous Procaine. Jefferson Hillman Hosp. Bull. (Alabama) 1949, 3 : No. 2 (Apr) 65-70

4. Brown, J. F.: Administration of Procaine Intravenously. U. S. Armed Forces M. J. 1950 No. 2 (Feb) 158-64

5. Cozen, L.: Intravenous Procaine as an Outpatient Proceedure. Indust. M. 1949 18 No. 11 (Nov) 487

6. Doak, E. K., and Selke, O. O., Jr.: The Effect of Intravenous Procaine on the Electrcardiogram. Texas Rep. Biol. M. 1949, 7 No. 2 (Summer) 318-31

7. Gordon, R. A.: Application of Intravenous Procaine Treatment to Traumatic Surgery. Current Res. Anesth. 1950, 29 No. 1 (Jan & Feb) 54-6

8. Graubard, D. J., Robertazzi, R. W., and Peterson, M. C.: Intravenous Procaine: A Preliminary Report. New York State J. Med. 47:2187 (Oct. 15) 1947

9. Griffith, H. R.: New Anesthetic Drugs. Canad. M. A. J. Dec. 1950 533

10. Horan, J. S.: Intravenous Procaine. Hawaii M. J.: 1949 8 No. 4 (Mar-Apr) 276-8

11. Hulpieu, H. R., Cole, V. V., and Vieira, Z.: Blood Levels of Procaine and Para-aminobenzoic Acid Following the Use of Intravenous Procaine Hydrochloride in General Anesthesia. Anesthesiology. May 1950; 333

12. Kraft, K. A.: Intravenous Procaine. Canad. M. A. J. 57:350 (Oct) 1947

13. Long, J. H., Oppenheimer, M. J., Webster, M. R., and Durant, T. M.: Effect of Intravenous Procaine on the Heart. Anesthesiology 10:406-15 July 1949

14. Marton, R., Spitzer, N, and Steinbrocker, O.: Intravenous Procaine as an Analgesic and Therapeutic Proceedure in Painful, Chronic Neuromuscular Disorders. Anesthesiology Sept. 1949 629

15. McLachlin, J. A.: The Use of Novocaine as a Substitute in Postoperative Care. Canad. M. A. J. 383-6 (April) 1945

16. Mushin, W. W., and Rendell-Baker, L.: Intravenous Procaine, A Review. Lancet, Lond., 1949 1: No. 15 (Apr. 9) 619

17. Olsen, C. W.: Procaine as an Autonomic Crug. J. Nerv. Ment. Dis. 1949, 110 No. 5 (Nov.) 395-9

18. Rittrich, N. M., and Powers, W. F.: Intravenous Procaine in Thoracic Surgery. Anesth. & Analg. 27:181-96 July-Aug. 1948

19. Sachs, J. S.: Present Status of Procaine Toxicity. J. Oral Surg. 1949 7 No. 4 (Oct) 312

20. Schalit, I.: The Intravenous Use of Procaine. Med. J. of Australia. 1949 No. 7 Aug. 13 241-5

21. Schiff, L. F., and Schiff, L. J.: Anaphylactic Reaction to Intravenous Administration of Procaine. Anesthesiology 1949, 10 No. 6 (Nov.) 753

22. Schrum, D.: Intravenous Procaine in Children. J. Pediatrics S. Louis. 1949, 34 No. 4 (Apr.) 433-8

23. State, D., and Wangensteen, O. H.: Delayed Serum Sickness. J. A. M. A. 130:990-5 1946

24. Steinberg, B. L.: Intravenous Procaine; Its Effect on Liver Function in Man as Determined by Cephalin Flocculation Test. Anesthesiology 1949 No. 6 (Nov.) 739-42

25. Taylor, I. B., Stearns, A. B., and Kurtz, H. C.: Intravenous Procaine. Anesthesiology March 1950 185

26. Uhley, M. N., and Wilburne, M.: The Effect of Intravenous Procaine on the Electrocardiogram of the Dog. Amer. Heart J. 36:576-581 1948