EXPERIENCES WITH PROCAINE ADMINISTERED INTRAVENOUSLY* †

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During the past two years, the intravenous administration of procaine hydrochloride in weak concentrations (0.1 per cent) has become a popular therapeutic measure. It is by no means a new type of therapy, for as early as 1908 a Spanish physician, Goyanes (1), used the intra-arterial injection of procaine as a method of producing regional anesthesia of the extremities. In 1909, Bier (2), used solutions of procaine for the same purpose, but he chose to administer the drug intravenously. After elevation of the extremity an Esmarch bandage and tourniquet were applied. The solution of procaine was then injected into a vein distal to the tourniquet, thereby trapping the drug in that portion of the extremity requiring anesthesia. Leriche and Fontaine (3) in 1935, advocated the use of procaine administered intravenously for the treatment of arteritis obliterans. In 1937, Lewy (4) used solutions of procaine given intravenously in the treatment of tinnitus aurium. This therapeutic procedure has not proved to be routinely efficacious. More effective uses of procaine administered by the intravenous route were suggested in 1940 by Lundy (5) and by Burstein and Marangoni (6). Lundy (5) found that pruritus caused by jaundice was relieved by the intravenous injection of procaine in weak concentrations (0.1 per cent). During the same year, Burstein and Marangoni (6) reported their results on the preventive therapy of ventricular fibrillation induced by epinephrine during anesthesia produced by cyclopropane. In 1941, Leriche (7) extended his own previous work to include trial with many other vascular disturbances in addition to arteritis obliterans. Still another use of the intravenous administration of procaine hydrochloride was reported in 1942 when Breton and Guidoux (8) recommended its use in the treatment of idiosyncrasies to various drugs.

Late in 1942, one of us (R. M. T.) suggested that solutions of procaine in weak concentrations (0.1 per cent), as used by Lundy (5), might provide adequate analgesia for the transportation of battle casualties, and alleviation of pain when surgical dressings of burns were to be done. Major F. E. Davis, M.D., U. S. A. (9), and Captain P. W. Searles, M.C., U. S. A. (10), investigated the applicability of these rec-

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ommendations and submitted unpublished data to substantiate this concept. After a conference with Major R. A. Gordon, R.C.A. M.C. (11), he used this type of therapy in the treatment of battle casualties, and, in 1943, published a favorable report of his experiences in the treatment of burns. He found that the pain associated with burns was obviated without complicating, concomitant respiratory depressions which not infrequently accompanies the use of opiates. His report revealed that this method of controlling pain was particularly valuable in the management of burns in patients who had inhaled irritating smokes or gases.

These encouraging reports were followed by the enlightening results of the therapeutic application of Burstein’s and Marangoni’s (6) investigative and experimental work dealing with the treatment of cyclopropane and epinephrine-induced cardiac arrhythmias. Burstein (12), along with other anesthetists serving overseas, encountered numerous cardiovascular emergencies (hypotension, gross irregularities of cardiac function, decreased cardiac output with failing peripheral circulation, progressive cyanosis, shock) which were controlled by procaine hydrochloride applied topically, or administered by the intravenous route. The opportunities afforded anesthetists, serving on thoracic surgical teams (13) to administer procaine in 1.0 per cent concentration for the treatment of cardiovascular emergencies occurring during major intrathoracic surgical procedures yielded valuable information, and served to substantiate Burstein’s and Marangoni’s (6) original concepts. The objective of such therapy was to decrease irritability of the cardiac conduction mechanism in the presence of cardiac dysfunction associated with anesthetic and surgical procedures. The objective was achieved. It has since been advocated by one of us (R. M. T.) that if procaine hydrochloride in 1.0 per cent concentration is effective in combatting deleterious cardiac arrhythmias in the presence of an emergency, the use of weaker solutions of procaine (0.1 per cent) administered slowly (1.0 gm. in 1 hour) as a prophylactic measure (13), immediately before and during operative procedures involving intrathoracic structures likely to produce these untoward cardiac effects, is well advised. This principle has been applied in actual practice at the Hartford Hospital for one and one-half years with gratifying results. That weak solutions of procaine hydrochloride administered intravenously may serve as a substitute for morphine in the control of postoperative pain was favorably reported by McLachlin (14) in 1945. At a recent meeting of the New England Society of Anesthesiologists in Boston, Martin (15) and Peterson (16) discussed their experiences with the intravenous administration of procaine in weak concentration. Peterson’s (16) experiences with this type of therapy for patients suffering from spastic diseases and arthritis were enlightening and encouraging.

A direct outgrowth of the prophylactic use of solutions of procaine in weak concentration, prior to and during intrathoracic surgical procedures, has been the adoption of its use for patients who present rapid
and irregular cardiac rates, before or during general surgical procedures. Repeated beneficial effects resulting from the intravenous injection of procaine (in 0.1 per cent concentration) have been observed. Cardiac action has been stabilized at a normal rate and regular rhythm. The character of the pulse has been improved. Concomitant improvement in patients’ general condition has been noticed, not only in elderly, debilitated patients, but also in younger patients having severe cardiac disease, for whom immediate surgical intervention was necessary. It is our belief that this therapy was instrumental in rendering these patients operative and their postoperative courses uneventful. The effectiveness of this therapy is illustrated by the following case.

An elderly woman was admitted complaining of an intermittent, ach-ing pain in the epigastrium which did not radiate. Physical examination revealed that the heart was enlarged to the left, a systolic murmur, grade 2, was audible over the mitral area, values for blood pressure were 180 mm. systolic and 95 mm. diastolic, and an irregular mass was palpable in the right upper quadrant. The abdomen was tense and tender. A progress note written on the day before operation revealed that the blood pressure was 80 mm. systolic and 40 mm. diastolic, the pulse rate 110, the respiratory rate 40 per minute. The rectal temperature was 103.2 °F. The patient responded poorly to questioning. Following the administration of blood and plasma, her condition improved and surgical intervention was considered feasible. The attending surgeon wrote the following: “This elderly woman is very ill, having an irregular pulse, elevated temperature and a definite acute gallbladder, which may be ruptured. She is in such poor condition that one unit of plasma (500 cc.), 500 cc. of whole blood and two ampules of digifolin are being administered before she is sent to the operating room.” Because of the patient’s poor condition an abdominal block was performed, and cyclopropane was administered during the surgical procedure. As anesthesia was induced intravenous administration of procaine in 0.1 per cent concentration was started. The pulse continued to be irregular in rate, rhythm and volume for a time, but after thirty-five minutes had elapsed, it became regular. It remained regular thereafter. An acutely inflamed gangrenous gallbladder was removed, and the patient was returned to her room in a much improved condition. The pulse rate remained elevated, but the pulsations were strong and regular.

Equally effective results have been obtained in other patients who have presented this clinical picture.

The immediate and dramatic improvement which follows topical or intravenous administration of procaine in 1 per cent concentration for the management of major intrathoracic procedures led us to employ the same therapy for a similar clinical syndrome occurring during an operative procedure performed within the neck.

A 53-year-old white man entered the hospital with a diagnosis of esophageal diverticulum; he gave a five-year history of dysphagia and
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regurgitation. Bilateral superficial and deep cervical block was performed, following which pentothal sodium was administered intravenously to obviate the difficulties encountered by the surgeon owing to persistent swallowing. While considerable traction was being exerted on the esophageal sac, and the overlying muscles were being retracted, the anesthetist observed the development of bradycardia, hypotension and progressive cyanosis. Improvement of the patient’s airway did not relieve the cyanosis. Three cubic centimeters of procaine in 1 per cent concentration was administered in divided doses of 10 mg. each. Shortly after the administration of 3 cc. the pulse rate suddenly increased from the existing rate of 44 per minute to 124 beats per minute, the pulse pressure and blood pressure improved and the cyanosis was relieved.

It must be admitted that the immediate improvement might have been coincidental but there was no release of traction on the part of the surgeon. In fact, the procaine was administered and the emergency was overcome without the operator being notified. The remainder of the operative course was uneventful. The possibility that these findings might have been caused by pressure upon the carotid sinus is admitted.

Gratifying experiences have led us to alter our concepts with reference to the widespread employment of analeptics in the treatment of cardiovascular emergencies. Rest is a time honored, fundamentally sound principle which forms the basis of judicious cardiac therapy. To be guilty of whipping an already overtaxed or failing myocardium into fatiguing activity is to be guilty of injudicious therapy. The administration of a stimulating drug such as epinephrine, per se, to a patient whose heart is already overburdened is likely to put that cardiac musculature at complete and permanent rest. Probably more harm is caused by the employment of the so-called analeptic drugs in the treatment of cardiovascular emergencies than by any other group of drugs, especially when they are used without proper appraisal of the situation. The intravenous administration of glucose in distilled water or saline solution, whole blood or blood fractions to assure adequate cardiac filling, together with the intravenous administration of procaine in 0.1 per cent concentration to reduce futile activity associated with excess irritability, is warranted as a prophylactic measure. One hundred milligrams may be injected rapidly in case of emergency if the patient is under general anesthesia but the adoption of preventive practice in anesthesia is one of the certain methods of reducing the incidence of complications, not only during but following the administration of anesthetic agents. The avoidance of untoward physiologic states during the course of an anesthetic procedure is known to reduce the incidence of untoward postanesthetic sequelae.

Accumulating experience with the intravenous use of procaine hydrochloride during the past two years leads us to believe that it offers
real therapeutic and diagnostic value in the management of patients suffering from pruritus associated with jaundice, contact dermatitis and exfoliative dermatitis. With the exception of one patient who had persistent jaundice (six to eight weeks’ duration) and another who had Hodgkin’s disease, the intravenous administration of procaine in 0.1 per cent concentration has given relief from itching which has varied in duration from four to eighteen hours. This therapy has not only allowed these patients to obtain much needed rest, but it has served to prevent cutaneous infections by eliminating the persistent desire to scratch during sleep. Pruritus associated with contact dermatitis or exfoliative dermatitis may be due to prolonged administration of some of the analgesic or sedative drugs. It is, therefore, fortunate that a therapeutic procedure is available which can be offered to these patients when the necessity of administering analgesic or sedative drugs can be eliminated.

The optimum time to administer this intravenous medication is in the evening. Scratching during sleep is prevented, thereby shortening the period of recovery. In the management of a small series of such patients, the intravenous injection of procaine in 0.1 per cent concentration has proved to be an effective therapeutic procedure. Whereas numerous other types of therapy failed to give relief, procaine proved effective. The following brief abstract illustrates its efficacy.

A 78-year-old white man was admitted to the hospital with the chief complaint of a cutaneous rash of three months’ duration, accompanied by generalized pruritus. Physical examination revealed that his body was covered with an excoriated, dry maculopapular erythematous rash except for the abdomen which was studded with discrete red papules. He had been treated by his physician with numerous types of ointments, all of which tended to aggravate the condition. While in the hospital he was treated with starch baths, Lugol’s solution and phenobarbital. Because of the persistence of the pruritus the patient was seen in consultation by a member of the Department of Anesthesiology who advised the intravenous administration of procaine in 0.1 per cent concentration. Preliminary skin tests were performed, using 0.5 per cent solution of procaine hydrochloride, and were found to be negative. Subsequently he was given 1,000 cc. of procaine in 0.1 per cent concentration in normal saline solution, with excellent results. All other therapy was discontinued that evening at eleven o’clock, and the patient slept soundly all night. In the morning he was not only more comfortable but his mental attitude was greatly improved. The following evening this therapy was repeated, using 500 cc. of procaine in 0.1 per cent concentration in normal saline solution. Again the patient slept well. Because of the marked improvement following the intravenous administration of procaine, no other therapy was subsequently used except as specifically indicated. A definite therapeutic adjunct to the management of these dermatologic patients is suggested.
Success in the control of pruritus led us to employ procaine intravenously in the presence of urticaria associated with the administration of blood. A patient undergoing a major operative procedure for removal of a pancreatic cyst received 500 cc. of blood during administration of general anesthetic agent. Forty-five minutes later generalized urticaria consisting of edematous blebs developed. Administration of epinephrine was without avail. The condition existed two hours postoperatively. At that time procaine, 250 cc. of 0.1 per cent, was given intravenously and the urticaria disappeared within fifteen minutes. Subsequent cross grouping of the donor and patient proved that faulty matching was not a contributing cause of the urticaria.

Another patient, prior to and during cystectomy, received three transfusions and following each, urticaria developed. Prior to the fourth transfusion given in the postoperative period, it was decided to give 250 cc. of procaine in 0.1 per cent concentration in an attempt to eliminate the possibility of a fourth allergic reaction. This was done and for the first time there was no untoward reaction following the transfusion.

The management of patients suffering from burns offers the anesthetist a real opportunity to contribute to the comfort of these unfortunate people, irrespective of the severity of the burns. Because intravenous therapy is mandatory in their management and since the vehicle for its administration is already in use, the addition of procaine hydrochloride to the fluids to be administered intravenously is warranted. This therapy reduces or eliminates the frequently repeated administration of morphine, demerol and other habit-forming drugs. The site of action of the procaine is believed to be peripheral. Hence the therapy is effective at the very source of the discomfort. The case of a graduate nurse giving a previous history of fainting episodes, who was found unconscious, lying in a pool of scalding hot water, is presented. Deep second and third degree burns of the buttocks, thighs, legs, pubis, external genitalia, perineum and the right breast resulted. A neurologic consultant made a diagnosis of carotid sinus syndrome. Personnel of the Department of Anesthesiology saw the patient before the first debridement and change of dressings, and suggested that procaine in weak concentration be administered intravenously. Prior to the debridement, morphine sulfate, ⅓ grain, and atropine sulfate, ⅛ grain, were injected intravenously. The first injection of procaine was given immediately before and during the initial debridement and change of dressings. This theory provided adequate analgesia for the removal of the dressings and for the more superficial debridement. When the adherent, necrotic tissue overlying the more deeply burned areas in the vicinity of the gluteal folds, perineum and labium was debrided, the intravenous administration of pentothal sodium in 2.5 per cent concentration was required. For twenty-eight hours following this procedure, the patient complained of no pain and required no medication for
discomfort or for sleep. Subsequently, she received a total of twenty administrations of procaine intravenously. Some of these injections were made in amigen but not until amigen and procaine were found to be compatible when mixed and tested out in rabbits by members of the Department of Hematology and Pathology. On two occasions the procaine was purposely omitted from the amigen without informing the nurse in attendance. Both "placebos" were followed by frequent complaints of pain which necessitated the administration of narcotics. Following the second "placebo" the patient volunteered the information that "last night's intravenous did not make me feel as relaxed as usual." By varying the type of fluid administered to this patient any evidence of fluid imbalance was avoided. Normal saline, glucose 5.0 per cent in distilled water and amigen were the fluids used.

The sympathetic effect is a definite and early action of procaine when administered intravenously. The following case-history is that of a man aged 41, who had been entirely well until five to six weeks before admission at which time he began to have severe pain in the left lower leg. The leg was somewhat swollen and warm. Approximately one week before admission he complained of the same severe pain in the right leg which began in the thigh and gradually spread down to the calf. At the time of admission, he was unable to walk without crutches because of the excruciating pain. The attending surgeon's diagnosis was thrombophlebitis (acute) of the right femoral vein, and subsiding thrombophlebitis of the left femoral vein. The patient's temperature for the first four days ranged up to 101 F. His sedimentation rate upon admission was 49 mm. per hour. Penicillin was not administered as it had been employed previously without effect. Two lumbar sympathetic blocks were performed by members of the Department of Anesthesiology, one on the evening of admission, and the second three days later. Relief of pain was immediate and the color of the right leg improved remarkably. Approximately one hour after completion of the first lumbar sympathetic block the patient was given 1,000 cc. of 0.1 per cent solution of procaine in physiologic saline solution in an attempt to prolong the effectiveness of the sympathetic block. This objective was achieved. It was apparent that there was noticeable improvement in the color of the left leg. Before the administration of procaine intravenously the entire left leg, which had been the site of the original pathologic process, presented a diffuse, mottled cyanosis. Within thirty minutes after starting the intravenous infusion all evidence of cyanosis had disappeared except for that of the nail beds. A total of nine intravenous administrations of procaine in 0.1 per cent concentration was given. During the acute stage of the disease the infusions did not completely abolish pain, but in the patient's own words, "the pain is reduced to an ache which does not bother me."

The surgeon's discharge note contained the following interesting information: "The intravenous infusions of 0.1 per cent procaine
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seemed to be of more therapeutic value than the sympathetic blocks.” Our appraisal was not as enthusiastic, but we do believe that the intravenous therapy was of decided value. His temperature returned to normal and the sedimentation rate decreased to 20 mm. per hour within five days. The patient was kept in bed for two weeks and was discharged on the fifteenth day. At that time, he was comfortable and the leg was apparently normal. It is interesting to note that the original thrombophlebitis of the left leg had incapacitated the patient for a period of five weeks whereas for the second attack his stay in the hospital was fifteen days.

Our experience in the treatment of skeletal muscular spasm is not extensive but our results indicate that it is worthy of trial. The history of a twenty-five year old woman who complained of backache for two years’ duration is presented. The patient was injured in an automobile accident in August, 1945, suffering fractures of the transverse processes of the first, second, third, and fourth lumbar vertebrae; fractured ribs and contusions with formation of hematoma of the left dorsolumbar region. Following discharge from the hospital, the low back pain had been a constant complaint, whereas the pain which extended down the left leg was of but five months’ duration at the time members of the Department of Anesthesiology saw this woman in consultation. Neurologic examination performed soon after the more recent admission emphasized the following: “Marked nervousness, pain, touch and temperature sensations are diminished over the course of the left lateral cutaneous nerve. Muscle spasm is present in the lumbar area, and there is pain and difficulty associated with attempts to raise the left leg.” Physiotherapy, general medical care and prolonged bed rest were followed by no marked improvement.

On March 10 of this year one of us (C. M. B.) saw the patient in consultation at the suggestion of the orthopedic surgeon in attendance and performed a therapeutic high caudal block. Forty cubic centimeters of procaine in 1.0 per cent concentration followed by 40 cc. of normal saline solution was injected into the caudal canal. There was immediate relief from the pain in the lumbar region and from that which extended down the left leg. The latter pain has not recurred, but as soon as the effect of the procaine had worn off, the pain in the lower back returned. Two days later the patient received her first intravenous injection of procaine in 0.1 per cent concentration. This resulted in some relief from pain for a period of four hours. The second intravenous infusion containing 0.1 per cent procaine in physiologic saline solution brought about more marked relief from pain. On the fifth day of treatment a second high caudal block was performed at the request of the surgeon. The pain in the lumbar region was again entirely relieved by the block, but recurred in five hours. That evening the third administration of procaine in 0.1 per cent concentration was given. During the next two days she received additional injections of
1.0 Gm. of procaine hydrochloride in 1,000 cc. of normal saline solutions. On the seventh day of treatment she stated that the pain in the dorsolumbar region was not as severe, and that she could move about the bed more freely and without as much pain. After eleven days the patient had received six intravenous administrations of 0.1 per cent procaine in normal saline solution or 5 per cent glucose in distilled water. At this time, she was more active in that she turned from side to side without discomfort, walked better and was up about the ward for longer periods of time. The physiotherapists noticed greater range of movement. Her appetite improved. It must be admitted that psychotherapy played a part in the improvement noted in this chronically ill patient, but we believe that the intravenous therapy deserves a fair share of credit.

Patients who receive solutions of procaine by the intravenous route frequently volunteer the information that shortly after the therapy is started, "a comfortable, relaxed feeling becomes manifest, accompanied by a generalized sensation of warmth." Minor degrees of drowsiness and sleepiness are nearly always evident. The depressant action upon the central nervous system is minimal. Although mild dizziness has been a common complaint during the early part of the injection, the more alarming signs and symptoms of toxicity to procaine have not appeared. It has been our experience that the dizziness has been a transient complaint, and that with the continuance of the therapy the vertigo frequently subsides. Pentothal in 2.5 per cent concentration is always kept in readiness at the time of administration. To date, we have not used pentothal to combat reaction to procaine in the course of its intravenous administration. We believe that this record is significant and that it substantiates our plan to employ procaine in 0.1 per cent solution for intravenous injection at a rate never exceeding 1,000 cc. in one hour.

Evaluation of the therapeutic value of the intravenous administration of procaine hydrochloride in 0.1 per cent concentration leaves one with the distinct impression that our present knowledge of the pharmacology of this anesthetic agent is far from complete. Although it is believed that in the presence of trauma procaine exerts its main action within the tissues that are damaged, its true mechanism of action is not known. Additional investigative work is necessary, but sufficient clinical trial has already been undertaken to warrant its use in clinical practice. We particularly appreciate the availability of a drug which can be used in emergencies associated with cardiovascular dysfunction. Preliminary reports concerning the effectiveness of weak concentrations of procaine administered intravenously to patients suffering from trauma are encouraging. It is, therefore, encouraging to believe that this therapeutic procedure may be of real value in the management and control of the many children and numerous veterans who are suffering
from congenital and acquired spastic states. Our extended efforts in
their behalf are warranted.

We wish to offer words of caution in regard to the employment of
concentrated solutions of procaine. The drug is a convulsant. Its use
in concentrated solutions or rapid injection of dilute solutions may
cause untoward reactions that will not only jeopardize patients' lives
but will bring this agent and method into disrepute. It would be dis-
couraging if this should occur before its field of usefulness is ascertained.

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