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Intravenous procaine in the treatment of the arthritides

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Subject Index

The History of Intravenous Procaine

Since the synthesization of procaine hydrochloride by Einhorn[1] in 1905, the accidental injection of this drug into the blood stream has been feared as one of the principal causes of toxic reactions during local anesthesia. Originally, procaine was developed as a substitute for the more toxic local anesthetic, cocaine, and introduced under the trade name, "novocaine".[2]

The intravenous administration of procaine has attracted sporadic attention from the medical world since August Bier[3] in 1908, presented a paper entitled, "On a New Method of Producing Anesthesia in the Extremities".[4] Briefly, his technic consisted of elevation of the extremity followed by the application of tightly-wound Esmarch bandages to express the maximal amount of blood from the limb. The bandages were wound tightly in a spiral fashion from the distal to the proximal end of the extremity, then a tourniquet was applied over the proximal termination of the bandage. The proximal bandage was then unwound to expose the site of operation, while the tourniquet above prevented re-entry of the blood or escape of the anesthetic agent into the general circulation. A 0.5% solution of procaine, in dosages ranging from 50 to 100 cc., was administered via the superficial veins, usually the antecubital.[5] Following operation, the veins were thoroughly irrigated with normal saline solution to remove as much of the procaine as possible, then the bandages and tourniquet were loosened slowly to prevent the remaining procaine from reaching the general circulation too fast.[6] Bier's procedure was somewhat complicated, and carried the danger of accidentally subjecting the patient to a lethal concentration

of the drug.[7] A modification of the original intravenous technic of Bier is being practiced today by Herreros[8], of Mexico, under conditions far from favorable, but with gratifying results.

In this same year, 1908, a Spanish physician, J. Goyanes,[9] used the intra-arterial injection of 0.5% procaine as a method of producing regional anesthesia in the extremities. He, like Bier, obtained adequate anesthesia for surgical procedure, but the inaccessibility of arteries proved to be a marked disadvantage in the employment of his technic.

Neither method was widely accepted, and about this time vasopressor drugs were added to solutions of local anesthetic agents to produce local ischemia. This resulted in a sharp rise in the mortality rate, with consequent abandonment of the intravenous route. Martin[10] suggested that the cause of death following procaine-epinephrine injection was due to the epinephrine. However, procaine itself is toxic, and its toxicity is tripled by the addition of epinephrine.[4]

Leriche and Fontaine[11], in 1935, advocated the use of intravenous procaine in the treatment of endarteritis obliterans, and in 1937, Lewy[12] used local anesthetics intravenously in the treatment of tinnitus aurium. In 1940, Lundy[13] employed this procedure to relieve the pruritus associated with jaundice and obtained favorable results. Further work by Burstein and Marangoni[14] in 1940 demonstrated intravenous procaine to be of value in the preventive therapy of ventricular fibrillation induced by epinephrine during cyclopropane anesthesia.

In 1941, Leriche extended his previous work to include trial

with other vascular disturbances in addition to endarteritis obliterans. Still another use for procaine, administered intravenously, was reported in 1942 when Breton and Guidox[15] recommended its use in the treatment of idiosyncrasies to various drugs. In 1943, Gordon[16] reported on his experiences with intravenous procaine to procure analgesia in burns, and the following year, Barber and Madden employed a 2% solution of procaine to lessen the occurrence of fibrillation during anesthesia. McLachlin[18] administered the anesthetic agent intravenously in 1945 for the relief of postoperative pain. During 1946, Burstein and Alexander[19] related their experiences with 1% procaine intravenously for the cardiac arrythmias occurring in chest surgery, and Allen, Crossman and Lyons[20] reported on the use of intravenous procaine for general anesthesia. Since that time, the use of procaine intravenously has become more general.

Knight[21] has employed procaine with sodium pentothal and curare in a great variety of cases and reports satisfactory results. It is to be noted however, that his doses of procaine were small.

Since 1947, Dr. David J. Graubard and his associates[4] have been the most prolific contributors to the literature on the subject in general, and particularly in regard to the treatment of the arthritides with intravenous procaine analgesia.

Pharmacology

Description: Procaine is para-aminobenzoldiethylaminoethanol hydrochloride, occurring as a white crystalline powder or as colorless crystals. Soluble in one part of water, in which its reaction is neutral, it is stable and does not decompose at temperatures as high as 100° Centigrade.[4] Three salts of procaine are available: the hydrochloride, borate and nitrate. Only the hydrochloride salt is official in the U.S.P., the other two being N.N.R. preparations. These salts are practically identical in action, and are marketed with or without epinephrine in a wide range of dosages and concentrations.[1]

Fate: When procaine is injected intravenously, it is rapidly hydrolyzed by an enzyme, procaine esterase,[22] into para-aminobenzoic acid and diethylaminoethanol, with subsequent acetylation of the former. Nearly 95% of the injected procaine can be found in the urine either as para-aminobenzoic acid, para-aminohippuric acid, para-aminobenoylglycuronate and diethylaminoethanol, or even as traces of procaine hydrochloride. Procaine, or one of its hydrolytic products, has been shown to be removed from the blood stream in twenty minutes and equilibrium is reached between the blood and the tissues. These products are also hydrolyzed or destroyed in the liver, and are excreted by the kidneys within ten to twelve hours following infusion.[4]

The enzyme, procaine esterase, was described as a constituent of the blood plasma by Goldberg, Koster and Warshaw[22] in 1943. The same year, Kisch[23] demonstrated that this enzyme, like cholinesterase, is inhibited by eserine and prostigmine, but the amounts of procaine

destroyed by this enzyme are so small that its clinical significance was considered minimal. Dunlop[25] found that blood had no destructive effect upon procaine, and concluded that the liver destroys it more rapidly and efficiently than do other organs. Isenberger,[2] in 1949, took issue with this view and stated that procaine esterase was apparently present in the blood plasma, probably formed by the liver, and capable of destroying procaine to the extent that injection of the procaine esterase inhibitor, prostigmine, might cause instantaneous death from procaine without any preliminary phase of convulsions.

Mode of Action: Although the present knowledge of the actions of procaine given intravenously or otherwise is far from complete, the theory appears valid that procaine circulating in a low, symptomless concentration in the vascular tree does not produce anesthesia or analgesia in normal tissues. However, in regions of inflammation and edema, the increased capillary permeability allows it to diffuse into the tissues and anesthetize the nerve endings there.[26] Plasma leakage at the site of injury allows an escape of procaine into the area which is seven to ten times more concentrated than in normal, uninjured areas. Any cases of pain not associated with this special vascular permeability will theoretically not be relieved by procaine infusion.[27]

That which gives intravenous procaine a special, constantly-increasing place in therapeutics is the aggregate of actions which it exerts simultaneously: analgesic, sympatholytic and vasodilating; secondarily, parasympathetic and anti-contracting. Procaine, as other nerve depressants, has a special affinity for the sensory

components of nerve fibers. Procaine base is liberated in the slightly alkaline body fluids and becomes lipoid soluble. By reversible combination with nerve protoplasm, the procaine first attacks the sensory nerve fibers because they are smaller and have thinner myelin sheaths. In this manner, differential penetration of procaine in proper concentration may completely block sensation before abolishing transmission of motor impulses.[28]

When procaine is employed intravenously, the modality of pain disappears first, followed by the sensations of cold, warmth and touch.[1] However, according to State and Wangensteen,[29] the vasoconstrictor reaction is paralyzed first, then progressively the sensations of cold, warmth, touch, tickling, pressure, pain, and finally "joint sense". Adams[6] lists the disappearance of the modalities in this order: temperature, pain and touch, with their reappearance in the reverse order.

In 1946, State and Wangensteen[29] suggested several possible explanations for the analgesic effect of intravenous procaine which include: (1) Potentiation of the normally secreted epinephrine content of the body. (2) Direct action 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. They further postulate that impulses may be inhibited by the neutralizing effect of procaine on acetylcholine, and more directly, the procaine may penetrate nerve tissue because of its lipoid solubility or decrease the oxygen consumption and interfere with the oxidative metabolism of the nerve cell.

In traumatized or inflamed areas, intravenous procaine has a

two-fold action: (1) direct action on the irritated nerve fibers, and (2) indirect action of diethylaminoethanol on the vascular endothelium. The modus operandi at the capillary bed may be considered as a competition between histamine and diethylaminoethanol for a given site of action or receptive substance, or the action might be explained from the clinical observations on a cholinergic-type response. The action of diethylaminoethanol is still under study.[4]

Moore[30] has demonstrated experimentally that pain results when a stimulating agent is permitted to reach the capillary bed in effective strength. The histologic demonstration of sensory nerve endings in the intima of arteries or on capillary endothelium is still a matter of controversy. If it is assumed that pain endings are located in the intercellular spaces of the peripheral tissues where they are reached by an irritant as a result of capillary permeability, then sensibility is not arterial, but resides in the tissues adjoining the capillary bed. Without taking into account the cellular components of the blood vessels, permeability of the capillary membrane depends upon an intercellular cement and on an adsorbed layer of protein which can be affected independently or concurrently by changes in the fluids bathing either side of the capillary.[31] Changes in the hydrogen ion concentration and calcium content of the medium will vary the permeability, for the cement behaves as though it were a reversible calcium salt of a weak acid, probably a proteinate. Vitamin C is necessary for the synthesis of this cement substance, and should be administered with procaine to those who are aged or suffering from malnutrition. In brief, the salutary effect of intravenous procaine therapy in the pathologic state is based on the permeability of the capillary membrane to colloids as well as to ions.[32,33,54]

Tissue response to trauma is a defense mechanism, and the vasospasm and exudate attendant upon the site of injury usually subside as the healing process is completed. If they persist, these conditions become an irritative focus. Intravenous procaine causes an interference with the reflex arc which produces pain, spasm and edema. Prolonged stimulation of pain fibers which reach the injured sensory neuron through an antidromic reflex may be self-perpetuating in a vicious cycle of reflexes. The constant circling within the internuncial pool involves the sympathetic motor neuron cells in the lateral horn of the spinal cord. It has been observed that vasospasm in the arteriolar and venular portions of the capillaries increases the filtration pressure, and edema and swelling appear. The capillary permeability and edema are also increased by hypoxia and cyanosis. Interruption of the reflex cycle seems to be the most logical approach to the problem of preventing severe vasoconstriction and edema. Treatment brought directly to the primary neuron by means of local infiltration has been successful, although this method has the disadvantage of being incomplete in an extensive area of trauma and frequent repetition is necessary to control "after-pains".[34,35]

The vascular approach can be expected to bring more rapid and longer lasting relief from pain because increased capillary permeability at the site of injury permits a much greater concentration of procaine than is possible in normal tissues.

Toxicity and Sensitivity: While the toxicity of intravenous procaine, administered over a short period of time, is known to vary in different animal species, the lethal dose for man is not known. Toxicity in man depends upon the percentage concentration, toxicity increasing

geometrically; hence, the amount, concentration and rate of administration must be considered.

In practical use, the toxicity of a local anesthetic depends upon the ratio between the rate of absorption and the rate of destruction. Procaine is only one-fourth as toxic as cocaine, either after intravenous or subcutaneous injection, despite the fact that procaine is destroyed much more rapidly in the body.[1] As late as 1941, Goodman and Gilman stated that, after intravenous injection of procaine, the lethal dose of the drug bore no predictable relationship to the rate of destruction because a lethal concentration was immediately reached in the body.

Hazard [28] states that the toxic effects of procaine are exerted primarily upon the bulbar centers and that it is dangerous to make injections near nerve centers, explaining in part the frequency of accidents encountered in urology and otorhinolaryngology. He further states that the mucous membranes, very vascular regions, the lungs and trachea have the ability to absorb procaine very rapidly. Goodman and Gilman certainly do not corroborate this statement, particularly in reference to the mucous membranes.

Ten minutes is sufficient time for the body to detoxify 60% of a lethal dose of procaine, the liver being particularly active in the detoxifying process. This rapid process of detoxication allows large amounts to be injected intravenously, provided the amount, concentration and rate of administration are carefully controlled. The addition of glucose to the procaine-saline solution allows a further margin of safety, as has been demonstrated with cocaine in animal experiments. One must remember that cocaine causes vasoconstriction and is therefore slowly absorbed, whereby procaine causes vasodil-

dilatation and gains more ready access to the circulation. If absorption is slowed, the toxicity of procaine is greatly decreased as it is rapidly destroyed by the liver.[1]

Following rapid intravenous administration, quick hydrolysis may not be adequate to prevent accumulation of dangerous levels of procaine in the blood and vital tissues. Procaine diffuses rapidly and tends to develop toxic concentrations. Signs and symptoms of toxicity may develop rapidly; the early phase of stimulation may be transitory or absent entirely, to be replaced or followed by sudden circulatory and respiratory failure. Obviously, it should be used in the lowest effective concentration and in the least total amount compatible with the purpose for which it is used.[2] The intravenous administration of procaine has advantages over methods in which the rate of absorption is uncontrollable, as it can be begun cautiously, halted at any sign of danger, and is destroyed in the circulation within a few minutes.

The minimal lethal dose of intravenous procaine varies with animal species:[36] from 40-60 mg./kg. in the rabbit;[37] from 40-45 mg./kg. in the cat;[38] 40 mg./kg. in the guinea pig;[39] and 62.4 ± 14.6 mg./ kg. in the dog.[40] As stated above, the lethal dose for man is unknown.

Although procaine is the least toxic of all the local anesthetics, it sometimes causes systemic effects in unusually sensitive individuals. Deaths have been reported following the injection of from as little as 0.01 to 0.13 grams of procaine. Such responses are probably due to idiosyncrasy and fortunately are rare. Death is usually characterized by cardiovascular collapse and occurs immediately following administration. Some individuals are extremely

susceptible to the stimulation of the central nervous system which procaine may produce. The reaction is slow in onset and can be completely controlled by the use of barbiturates.[1]

In the clinical use of intravenous procaine, routine tests for sensitivity to the drug are made. Less than 1 cc. of a 1% solution of procaine is injected intradermally; in sensitive individuals, a local reaction with systemic signs of agitation and dyspnea occur within ten minutes. If there is any doubt about the reaction after fifteen minutes, a drop of the solution may be instilled in the eye, as the conjunctival reaction can scarcely be serious if the skin reaction is at all questionable.[26] Although instances of hypersensitivity are rare, use of the drug intravenously is not recommended without previous testing.[28] Lewy made intradermal cutaneous tests on his first group of patients, but stopped the practice since he felt that it was an unwarranted assumption that patients having a cutaneous sensitivity to procaine would necessarily have a general reaction. However, procaine was found responsible for a true cutaneous sensitization in a recently published case.[28]

Many contributors to the literature, including Graubard and his associates, contend that there are no contraindications to the use of procaine intravenously.[41] Certainly it should not be used in hypersensitive persons, rare though they might be. Old or yellowed solutions should not be used, as procaine in aqueous solution loses its activity in six months. Intravenous procaine should never be given after subcutaneous administration of morphine sulphate, since the alkaloid reduces the tolerance of the body to procaine; nor after treatment with epinephrine, as the latter reduces or completely counteracts the therapeutic effects of procaine. The toxic effects of other drugs used at the

same time must be considered, as procaine is incompatible with silver salts, caustic alkalis and their carbonates, soaps, iodine and iodides.[28] There is some evidence to suggest that intravenous procaine is contraindicated in cardiac disease, especially when digitalis or digitalis-like substances are used.[41] Adams[6] states that intravenous procaine should not be employed in patients with advanced arteriosclerosis or for operations involving diabetic or senile gangrene. Procaine is antagonistic and incompatible with the sulfonamides, lobeline and hordenine when administered intravenously.[28]

Signs and symptoms exhibited by the patient during the administration of procaine intravenously vary from patient to patient, but in general are these: a feeling of warmth throughout the body five to seven minutes after the start of the infusion; this sensation is sometimes accompanied by a flush over the head, face and neck, except for marginal circumoral pallor.[43] This is followed by dryness of the mouth, metallic taste, lacrimation, light-headedness and dilatation of the pupils. There may also be mental confusion, thick speech, dizziness, nausea, pounding in the ears, minor inebriety, and there may be a sensation of heaviness in the abdomen which is temporary and causes no distress to the patient. The latter sensation may appear several times during the course of the infusion and is apparently related to the rate of injection.[44] Many patients feel comfortable and relaxed with the alleviation of pain, but increasing the rate of flow or the concentration of the procaine solution may result in the manifestation of apprehension, vertigo, sensation of trembling, and sleepiness beyond the point of comfortable relaxation. Most patients are cheerful and on their feet with-

in fifteen minutes after the completion of the infusion. Untoward actions of procaine are reflected by the bulbar centers and inhibition of respiration leads to progressive dyspnea, the patient loses consciousness, and convulsions precede death.

Moderate tachycardia may develop, but alarming changes in respiration, circulation, and other vital functions were not observed by Allen.[26] Larger doses may cause the appearance of the signs and symptoms noted above, and in a few, convulsions developed with the rapid infusion of strong solutions. The spasms were brief and subsided a minute after halting the infusion. Mere overdosage is apparently not at fault; in some cases, convulsions returned with every attempt to speed up administration and hence, anesthetic and convulsive thresholds are nearly identical in such patients. These convulsions are recognized as a serious and conceivably prohibitive handicap to the method. Epinephrine is indicated for respiratory and circulatory distress; intravenous barbiturates, as soluble sodium luminal, for convulsive states.[41] With or without treatment, convulsions subside in a minute, as a rule, after stopping the infusion. There are two methods them, of controlling or preventing convulsions: (1) premedication with the barbiturates, and (2) stopping the infusion at the first sign of twitching of facial or other muscles, increased reflexes, or other indications of impending convulsions.[45]

Ameuille gave 5000 infusions of procaine intravenously over a period of 50 months and witnessed epileptiform crises with mental excitement, sometimes with temporary loss of consciousness, only three or four times.[42] Graubard reports two instances of momentary unconsciousness in more than 2000 infusions, but at no time were

sedatives, oxygen, or restorative drugs necessary. He has seen no instances of sensitivity and recognizes no contraindications to the use of the drug.[43]

During the intravenous administration of procaine, there is an accelerated pulse and respiratory rate, and a slight lowering of the blood pressure, especially in hypertensive patients.[46] Increased diuresis with 150-300 cc. of clear urine is excreted in the first 30-60 minutes following the infusion, the effect sometimes being maintained for 24-36 hours.[42] There is a decrease in the body metabolism, a slight fall in body temperature, a slight elevation of the normal glycemia and an increased epinephrine hyperglycemia. Beutner[47] reports no depression of cardiac activity despite the fact that procaine produces widespread vasodilatation. Red blood-cell sedimentation rates, blood counts and chemical analyses of 17 different constituents of the blood fail to show any deviation from normal values.[41]

Dosage: In determining dosage, one must consider the amount, concentration and rate of administration of the procaine solution. As stated previously, the dosage necessary to produce a given effect varies with the individual. Since the death of experimental animals was contingent upon critical concentrations of procaine in the circulating blood producing central medullary paralysis, it was considered that the total amount injected should be well below the minimal lethal dose in animals, or 40 mg./kg. of body weight.[48]

Various clinicians have employed intravenous procaine in concentrations as high as 2%, in a wide range of total dosage. The structural similarity between diethylaminoethanol and benadryl prompted

Graubard and his associates to employ the dosage of benadryl in children, and therefore chose the amount to be given at one time to be 4 mg./kg. of body weight. The procaine is diluted to 0.1% or 1:1000 solution with isotonic saline; thus, one cc. of solution contains one mg. of procaine. Preparation of the solution is effected by adding five cc. of a 20% solution of epinephrine-free procaine hydrochloride to 1000 cc. of isotonic saline solution. Old or yellowed solutions are not used. The solution is vigorously agitated to insure uniformity of the solution prior to injection. A 0.2% solution was tried, but more side effects were observed.[42]

For simplification, the term "procaine unit" was devised; this is the amount of procaine, calculated at 4 mg./kg., to be given in twenty minutes in a 0.1% solution. For example, a 70 kg. man would receive 280 mg. of procaine in 280 cc. of isotonic saline in twenty minutes, or at the rate of fourteen cc. per minute. Knowing that procaine, given intravenously, could no longer be identified as such or as para-aminobenzoic acid after twenty minutes, and that the sudden injection of large amounts would not be tolerated, Graubard concluded that the total amount of procaine-saline solution should be administered over this particular period of time. The total dosage varies from 200-300 cc., the interval between infusions being determined by the general condition of the patient, and the nature and status of the disease process under treatment.

The ordinary intravenous drip apparatus may be used, but to maintain an accurate and even rate of flow, Graubard and Robertazzi devised a "flow-rater";[49] thus avoiding the toxic manifestations of overdosage and the non-effectiveness of underdosage. The "flow-rater" is an instrument wherein fluids are discharged under controlled

pressure head conditions through an annular aperture of controlled variable size. An orifice is formed between the periphery of the head of the float and the inside wall of the tapered tube in which it travels. The upward and downward forces acting upon the float are in equilibrium so that the float assumes a definite elevation at a given rate of flow. Inasmuch as the net weight of the float is the same at all elevations, it follows that the pressure drop across the float must also be constant. Since the tube is tapered, the annular cross-sectional area for flow is variable. Increasing flow rates, therefore, do not increase the pressure drop across the float, but cause it to take a higher position in the tube and thereby provide greater flow areas.

When using the 0.1% procaine and saline solution, the error factor in using the flow-rater is less than 0.5%, and the range of output is between 5 and 50 cc. per minute. The flow-rater is used with a 19-gauge needle and the infusion is given via the antecubital vein, regardless of the location of the lesion or lesions in question.[50]

Intravenous Procaine in the Treatment of the Arthritides

The tremendous progress made in most fields of medicine during the past decade has hardly altered the fate of the arthritic. The advent of intravenous procaine therapy, ACTH and cortisone has given considerable hope to physicians and patients alike. The physician seeks relief from a multitude of unsatisfactory therapies and an inflated, confusing nomenclature; the patient, from the pain and disability produced by the disease.

The constantly increasing and more extensive use of procaine hydrochloride intravenously has aroused considerable interest among many members of the medical profession since this mode of administration runs counter to accepted teachings and practice, and particularly since the results which have been reported thus far have been quite encouraging and satisfactory.

There are many signs and symptoms of arthritis, but the patient seeks medical aid primarily for relief of pain and spasm. Animal experimentation and increasing clinical experience suggest that the arthritic process depends partly on an imbalance within the neuroendocrine system. This imbalance apparently involves several factors of the system rather than a single dysfunction.[51,52]

The pain which accompanies arthritis is a result of, and dependent upon, anatomic, physiologic and pathologic factors. The articular cartilage itself is insensitive, so the pain is due to sec-

ondary changes wrought by contracture in the periarticular tissues and joint capsule.[49] When the abnormal stimulus irritates the tissue, the dysfunction in the capillary bed leads to increased capillary permeability, edema, vasospasm, anoxia or hypoxia, and changes in the hydrogen ion concentration in that area. As a result of these changes, metabolites accumulate in the interstitial tissue and pain is experienced by the patient. Normal tissue metabolism and fluid interchange is markedly interfered with, and the local vasospasm hastens the degeneration and necrosis of the affected tissues. When procaine is administered intravenously, it reaches the dysfunctioning capillary bed, anesthetizes the irritated sensory nerve endings and restores the normal circulation in the area by releasing the neurogenic vasospasm and by its own inherent vasodilating action.[2,47]

If an irritative process at the periphery persists, a central nervous system disturbance at spinal levels probably develops and irreversible changes are produced in the ganglia cells of the autonomic nervous system. We are forced to assume that these changes are the basis for other pathologic phenomena, as shown by the hyperactivity of the vasomotor apparatus in chronic polyarthritis. There is evidence to suggest a direct relationship between lesions of the autonomic nervous system and the disease process in acute and chronic conditions. Procaine, by depressing the irritating peripheral process, prevents undue stimulation of the sympathetic ganglia.[51] The action of procaine in influencing the humoral balance seems to depend upon its ability to inactivate cholinesterase,

thus allowing for the more sustained action of acetylcholine. The various theories and known actions of procaine have been discussed quite fully under the section on pharmacology.

The number of intravenous procaine infusions given any particular patient is governed by the general condition of the patient, the type and status of the disease process, and most important of all, the relief or freedom from pain. Some patients receive infusions daily, others receive them weekly or monthly, as required by their appreciation of this modality and their degree of physical disability due to spasm, contractures or ankylosis. There appears to be a cumulative effect accompanying therapy with intravenous procaine, for many patients receive lasting relief after a few infusions have been administered.

Arthritic patients are given 4 mg./kg. of procaine in twenty minutes, or fourteen cc. of procaine-saline solution per minute for twenty minutes as previously outlined. No morbidity, mortality, sensitivity or addiction to the drug has been noted as a result of over 3000 infusions given by Graubard and his co-workers.

For the sake of simplification, patients have been classified as having traumatic arthritis, osteoarthritis or rheumatoid arthritis. These clinical entities or diagnoses are based upon complete histories, physical examinations, laboratory investigation and clinical studies. It should be noted that in all cases, therapeutic efforts are directed toward analgesia, not anesthesia, because at no time is the patient rendered unconscious unless it be due to idiosyncrasy or overdosage.

Traumatic Arthritis: According to the most recently published works on this type of arthritis, the results from treatment with intravenous procaine have been very satisfactory. Graubard and Peterson[51] reported on a series of 22 cases receiving a total of 92 infusions, an average of 4.2 infusions per patient. Twenty were relieved of pain almost entirely, one obtained "fair" relief, and one received no benefit. All but the latter experienced increased mobility in the affected joints. The one case whose results were poor failed to return to the clinic following the first and only infusion. There is no reference made to total dosage or interval between infusions.

The majority of patients reported that pain returned four to six days following the first infusion, but that it was considerably diminished in intensity. The increase in mobility of the affected joint varied from complete restoration of function to partial increase, depending upon the anatomic structures involved, the pathologic changes present, the structural deformity, and the length of time the deformity had existed.[30] Increased mobility is not to be expected where ankylosis is in evidence; however, one case with almost complete obliteration of the joint space improved from approximately 50% of function to 95% in comparison to the unaffected limb.[51]

Graubard's first case of traumatic arthritis obtained increased mobility and relief of pain after fifteen infusions. Subsequently, he returned to work after a disability of one year in duration. Another typical case is that of a young man with traumatic arthritis of the elbow who was given 200 mg. of

procaine solution intravenously and received immediate relief from pain and increased mobility. The next week he began work requiring manual labor. Five months later, he returned for another infusion because of slight pain in the elbow, but without any loss of function. Again, he obtained immediate relief from pain.[49]

Berthelemy,[44] Moore,[30] and Tovell and Barbour[53] also report satisfactory results in traumatic arthritis after employing this type of treatment, but their reports are very brief and uninformative.

Osteoarthritis: An interesting and unexplained phenomenon occurs when treating patients afflicted with this disease, as an appreciable number will show no response to intravenous procaine therapy until after the 6th, 7th, 8th or even 9th consecutive infusion. It appears that the procaine has to overpower the irritated nerve fibers located more centrally before the peripheral neuron is affected.[51]

The imbalance of the autonomic nervous system produced by an irritative or toxic focus can explain many of the observations found in destructive arthritis of the hip: sensitivity to thermal changes, atrophy of the skin, hyperhydrosis and even flexion contractures and muscular atrophy. It has been stated that nature's "protective muscle spasm" is the gentlest and most effective form of immobilization since it decreases pain by decreasing function and by putting the affected joint in the most comfortable position. The loss of function is primarily due to

pain, which may be diminished or abolished by the proper use of intravenous procaine.[49,51]

In June, 1947, Graubard, Kovacs and Ritter[41] had treated nine cases of osteoarthritis with from two to sixteen infusions per patient. Duration of the disease varied from two to fifteen years. Following therapy, six of seven had relief of pain and increased mobility to the extent that they all returned to their occupations. The remaining cases in that series received only moderate or temporary relief from pain, although all had increased mobility of the affected joints. Exercise and manipulation of the joints after the infusions were performed with little or no pain. Dosages of 0.1% procaine-saline solution varied between 200-300 cc. per infusion, given at the rate of 10-15 cc. per minute.

In January, 1949, Graubard and Peterson[51] extended their series to include 110 cases of osteoarthritis. A total of 667 infusions was given these patients; an average of six infusions per patient, usually given three to four days apart. Relative to relief from pain, 89 responded well, 15 fair, and 6 poorly. The latter six were the only patients not gaining an increase in mobility. Vitamin C was added to the infusion in each case.

A male porter with severe pain from osteoarthritis in both hips with inability to bend, got about with the aid of canes on "good" days, with crutches on "bad" days. Roentgenologic examination showed marked bony excrescences in the acetabular regions of such degree that fusion of the hips was believed to be present. The patient was given 280 mg. of procaine by infusion, and

immediately following the first injection, pain was diminished and the thigh could be flexed on the abdomen at a 90° angle. The patient returned for twelve consecutive weekly treatments because he feared the return of pain. Following this twelve week course of intravenous procaine infusions, he returned to his job as a porter, required no canes or crutches, and gained ten pounds in two weeks.

From the diagnostic point of view, Graubard and Peterson have advocated the use of intravenous procaine as a differential diagnostic aid in cases of herniated intervertebral disc. These cases show no abatement of signs or symptoms after treatment, as might be expected in arthritis of the spine. This is typical of results in the pain syndrome due to a mechanical factor.[4,51]

Rheumatoid Arthritis: Equivocal results were reported in an early series of cases where intravenous procaine was employed in the treatment of this malady, but intensive therapy instituted later has produced gratifying results. Daily infusions of procaine and vitamin C, supplemented by parenteral intramuscular injections of 500 mg. of vitamin C for two weeks will usually produce sufficient relief from pain and spasm to allow physical therapy to be instituted. Relief from pain releases muscle spasm, thus improving flexion contractures so frequently found. The rehabilitation of the patient is of the utmost importance.[51]

In a series of 33 cases, each receiving an average of 8.3 infusions, 21 received marked benefit, 7 fair, and 5 received

poor response to therapy. Only seven experienced no increase in mobility. Of four cases of rheumatoid arthritis of the hip, one patient obtained temporary relief from pain and spasm with four infusions; duration of the disease was one year. The other three patients, in whom the condition had been present for 7, 10 and 12 years, had relief of pain and increased mobility, one returning to work; infusions totalled 15, 18 and 6, respectively. In two cases, dizziness and nausea persisted for 24 hours following the infusion; these cases had some form of hepatic dysfunction.[34,49]

The results obtained in a reported case of acute rheumatic fever, an allied disease, should offer some hope for those so afflicted. A 14-year-old girl had been bedridden for nine months following an initial attack of rheumatic fever manifested by pancarditis and polyarthritis. When first seen, all the major and minor joints of the extremities were involved, as manifested by pain, swelling, contracture deformities and limitation of motion. Radiographic examination revealed marked osteoporosis. The patient was given five infusions of procaine intravenously during an eight week period, in conjunction with adequate, supervised physiotherapy. At the end of this time, she was able to get about in a crawler and to use her hands and arms in simple maneuvers. Radiographic examination after treatment showed recalcification of osteoporotic areas.[51]

Vitamin C as ascorbic acid or sodium ascorbate is added routinely to all procaine infusions: one gram to 1000 cc. of isotonic saline solution. The benefits to be derived from this

addition are threefold: (1) the correction of capillary porosity which accompanies vitamin C deficiency; (2) the increase of resistance to any toxic side effects of procaine, particularly in patients in poor nutritional condition; (3) the correction of vitamin C deficiency which laboratory methods frequently reveal in arthritic patients.[43,54]

It is important to note that satisfactory results obtained from intravenous procaine treatment of the arthritides do not represent cures. Cure is as yet impossible since the exact cause of arthritis is unknown. Intravenous procaine is recommended solely as an adjuvant to the treatment of arthritis. It has the advantages of ease of administration, ease of control, and usually provides satisfactory relief from pain and spasm. It may well prove to be a golden spike in our armamentarium against this crippling, painful disease of the ages.

Intravenous procaine therapy is recognized as a safe procedure provided that its administration is properly controlled. The improvement noted in the relief of pain and spasm in arthritis warrants further investigation into this relatively new use of the drug.

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