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Intravenous procaine and its application in cardiac dysfunction

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INTRAVENOUS PROCAINE AND ITS APPLICATION IN CARDIAC DYSFUNCTION

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Intravenous procaine hydrochloride has now been employed in a diversity of conditions as a therapeutic measure. That which gives intravenous procaine a special, constantly increasing place in therapeutics is the aggregate of actions that it can exert simultaneously: analgesic, sympatholytic and vasodilating; secondarily parasympathetic and anticontracting. The employment of procaine intravenously should be considered as an adjuvant in treatment of selected traumatic, inflammatory and spastic conditions, and as a prophylactic measure prior to and during intrathoracic surgical procedures. In fact, it will be shown that such a procedure is a prophylactic measure in overcoming cardiac irregularities manifested during general anesthesia. These irregularities are overcome due to diminishing hyper-irritability of the cardiac conducting system and reverting a shifted pacemaker to the sinus node.

Procaine hydrochloride is the least toxic drug that is available, and that can be utilized in local infiltration, lumbar or intrathecal block, therapeutic nerve block, or intravenous injection. It is the safest agent for the above purposes; nevertheless, in its use occasionally the toxic effects have elicited respect, but not fear. The present employment of dilute solutions of procaine intravenously has thus far indicated there are no contraindications to the use of the drug, and that intolerance is minimal. It is indeed an advantage to have such a drug available, and particularly will this drug be appreciated

if it proves to be efficient in emergencies associated with cardiovascular dysfunction.

That which stimulates the writer's interest in the intravenous administration of procaine is the approach to patients with cardiac arrhythmias who must undergo surgery and anesthesia, and as a prophylactic measure to prevent cardiac dysfunction in surgery. The potentialities not only of procaine, but of new drugs and devices being successfully employed, is a further step in progress as concerns pre-operative preparation of the patient. Furthermore, it is noted in reviewing the literature that interest in the employment of intravenous procaine has resulted in the observation that many more cardiac arrhythmias occur in surgery, as detected by electrocardiographic studies, than are clinically observed by the anesthetist. This is only one example of the manner in which we may better care for the cardiac patient by more thorough study of drugs and procedures.

Einhorn (18), 1905, published his paper on the synthesis of procaine as a substitute for cocaine. Most of the experimental and clinical reports on pharmacology and toxicology which followed were mainly related to the subcutaneous use of the drug. However, the intravenous administration of procaine hydrochloride is by no means a new type of therapy. Bier (15) in 1908 read a paper entitled, "On a New Method of Producing Anesthesia in the Extremities". His method consisted of injecting procaine into a superficial vein in a given area of a limb which had previously been depleted of blood by the use of an Esmarch bandage and tourniquet. The method was not widely

accepted in England and the United States. At about this time vasopressor drugs were added to solutions of local anesthetic agents to produce local ischemia. The addition of the vasopressors to the local anesthetic agents resulted in a sharp rise in the mortality rate with consequent abandonment of the intravenous route. Epinephrine increases the toxicity of the procaine. The method of Bier was abandoned due to the fear that with removal of the tourniquet there was the chance of flooding the body with a sudden toxic dose.

Goyanes (19) of Spain in 1908, also obtained analgesia by the intra-arterial use of local anesthetic agents. Adequate anesthesia for surgical procedure was established by both Bier and Goyanes, but the inaccessibility of arteries was the disadvantage of Goyanes' technique. A modification of the original intravenous technique of Bier is being utilized today by Herreros of Mexico, under conditions far from favorable, with gratifying results. Until 1937, with these three exceptions, the intravenous administration of procaine has been accidental, in the course of a local infiltration or attempted spinal anesthesia, precipitating extreme anxiety for the patients' welfare and unfortunately, on occasion, medico-legal investigation.

Eggleston and Hatcher (11), 1916-1919, working with cats, reported that toxic effects of procaine were in direct proportion to the rate of introduction of the drug into the blood stream. They found that the injection of a sublethal dose produced an abrupt fall in blood pressure (believed to be due to

cardiac effect) and cessation of respiration, followed by brief but severe clonic convulsions. This sublethal dose could be repeated with procaine in twenty minute periods without evidence of accumulation. Also, continuous intravenous administration of the compound was tolerated when more than a lethal dose was given over a period of time. The heart rate was found to vary but was usually slowed. Death, when it occurred, was "apparently due to the nearly simultaneous paralysis of the heart and respiratory center". From their experience in vitro they believed that the breakdown of procaine was mainly in the liver.

Lewy (19), 1937, successfully treated tinnitus aurium by the intravenous use of local anesthetic agents. In September, 1940, Lundy (18) (19) relieved the pruritus of jaundice by using 1:1000 procaine intravenously. Also in 1940 Rovenstine and Burstein (19) reported laboratory studies of the prophylactic and therapeutic treatment of ventricular fibrillation with intravenous procaine during cyclopropane anesthesia. This work had been preceded by an interesting and significant observation published in a paper by Beck and Mautz (5) 1937, in which they stated: "Showers of stimuli sent in by surface dissection have produced ventricular and auricular fibrillation both experimentally and at operations on the human heart. One method for the control of reactions produced by surface stimulation is by the use of procaine or metycaine applied to the surface of the heart. Two cubic centimeters of five per cent procaine hydrochloride applied to the surface of the auricles and ventricles is effective in anesthetizing the surface of the

heart and blocking the entrance of stimuli". The recent revival in intravenous use of procaine probably results from the paper by Beck and Mautz entitled "The Control of the Heart Beat by the Surgeon, with Special Reference to Ventricular Fibrillation Occurring During Operation". Since this time there have been numerous observations and reports of reduced cardiac irritability by the systemic administration of procaine following Bursteins' (8) original report.

In 1943 Gordon (2) (18) (19) administered procaine intravenously to ten burned patients, obtaining analgesia of the burned area, but not of other parts, unless the other parts became edematous. The duration might be as long as six hours, and the degree was sufficient to permit changing dressings comfortably. Barbour and Madder (19), in 1944 used two per cent procaine intravenously to lessen the occurrence of ventricular fibrillation in anesthesia; Webster (19) in 1945, reported the intravenous use of procaine for the relief of post-operative pain. Allen (1) 1945, reported higher concentrations of intravenous procaine were successfully employed for obstetrical anesthesia. Burstein (9) 1946, related his experiences in successfully employing one per cent procaine intravenously for the cardiac arrhythmias occurring in chest surgery.

Procaine chemically is para-aminobenzoldiethylaminoethanol, soluble in one part of water in which its reaction is neutral. It is stable and does not decompose at temperatures as high as one hundred degrees Centigrade. When injected intravenously in

sublethal doses, two processes are initiated: (1) hydrolyzation of procaine by an enzyme into para-aminobenzoic acid and diethylaminoethanol; (2) the acetylation of para-aminobenzoic acid and the greater acetylation of diethylaminoethanol. The presence of an enzyme in human plasma which catalyzes the hydrolysis of the drug to para-aminobenzoic acid and diethylaminoethanol was reported in 1948 by Brodie, Leif and Poet (11). They have shown that when administered at rates of twenty to forty-five milligram per minute the procaine completely disappears from the blood stream in about two minutes, regardless of the duration of the injection. Also in fresh plasma in vitro eighty to one hundred per cent of the drug is broken down in two minutes. They concluded that at least in the human being the liver is not an important site for the transformation of procaine, and thereby disproved the belief of Eggleston and Hatcher (11) that the breakdown of procaine was mainly in the liver as previously stated. Koster (16) has likewise demonstrated the presence of the enzyme which hydrolyzes procaine into its component parts in blood, serum, and plasma, and has called this enzyme procaine esterase.

Of the two split products of procaine, diethylaminoethanol is not stable in metabolism, and usually can be quickly destroyed or detoxified. It is, moreover, more toxic than para-aminobenzoic acid, and in high concentration is capable of producing convulsions. It is also thought that diethylaminoethanol is the one responsible for undesirable effects. At the same time, it should be pointed out that in rapid administration,

especially of a concentrated solution, molecular procaine along with split products is found in the urine. Graubard (12) states that nearly 95 per cent of injected procaine is found in the urine as split products and traces of procaine. Undesirable effects may follow if there is something wrong with the physiologic detoxification mechanism, or if the speed and total volume of procaine are in excess of detoxification by normal processes.

Our present knowledge of the pharmacology of procaine is not complete, and its true mechanism of action is unknown. First it is important to recall the special affinity of procaine, and other nerve depressants for the sensory components of nerve fibers. Procaine base is liberated in the slightly alkaline body fluids, and in this form is lipoid soluble. By reversible combination with nerve protoplasm the procaine first attacks the sensory fibers because they are smaller, thereby exposing the largest surface area per unit of volume, and because they have a thinner myelin sheath. In this manner, differential penetration of procaine in proper concentration may completely block sensation before abolishing transmission of motor impulses. Since this effect is strictly local the anesthetic must usually be applied in such a way that an effective concentration reaches the nerve supply of the part which it is desired to affect.

This concentration of procaine reaching the desired part of the body may be effected on the basis of the present theory that regions of injury, inflammation, edema, and pain suffer increased capillary permeability, with sufficient diffusion of

procaine into the tissues for localized anesthesia of the nerve endings. The abnormally increased capillary permeability in injured regions has long been familiar, especially in studies of shock. In experiments, published between 1939 and 1943 (2), large intravenous injections of either plasma or salt solution resulted in huge fluid accumulations in the injured parts, but not elsewhere in animals with traumatic shock; and no comparable exudation was caused by such injections in animals with hemorrhagic shock. These findings have been confirmed by investigators having facilities for demonstrating the special permeability in traumatized tissues by injection of identifiable substances, such as foreign protein or radioactive compounds. Perhaps there has been a failure to perceive or follow up the wider therapeutic implications of these facts.

Permeability is evidently a dominant factor in the distribution of substances in the body. The increased permeability of injured or inflamed tissues presumably accounts for the specially high concentration of drugs, such as salicylates, in such tissues as observed by pharmacologists. In the same manner, all reports of analgesia which has been obtained in treatment of selected traumatic, inflammatory and spastic conditions conform precisely to the theoretical expectation; namely, relief of pain by transudation of procaine in areas where capillary permeability is increased, especially when the procaine is administered with considerable fluid intravenously.

Any cases of pain not associated with this special vascular

permeability will theoretically not be relieved. It likewise still appears valid that procaine circulating in a low symptomless concentration in the blood does not produce local anesthesia in normal tissues. It is believed that in traumatized or inflamed areas procaine administered by the intravenous route has a twofold action(12): (1) direct action on the irritated nerve fibers; (2) an indirect action of diethylaminoethanol on the endothelium of blood vessels. This describes the dominant peripheral action of procaine, but central nervous system effects are under study also and appear to increase as the dosage increases.

Inasmuch as the subjective disturbances of dizziness, blurred speech or mental confusion were unaccompanied by signs of danger in circulation or respiration, Allen, Crossman and Lyons (2) increased the intravenous dosage until it led actually into a new field of study, namely procaine anesthesia of the central nervous system. This development was made first by Allen (1) in obstetrical cases as previously mentioned. When intravenous procaine is employed, the range between analgesia and anesthesia varies, and the range between anesthesia and convulsions is narrow. Unless this range can be widened its usefulness will be limited. This may be accomplished to some extent by the use of pentothal and possibly other additive agents, such as one of the curarizing drugs, or other antimyotatic agents.

From the experiments of Long et al (20) who studied the effects of intravenous procaine on the dog heart, the action

of procaine on bulbar centers was observed. They concluded from their experiments that the dog dies a cardiac death only if the injected dose of procaine is sufficient to cause ventricular fibrillation. In most cases respiratory failure occurred first; the blood pressure might be in the range of 10-30 mm. of Hg. and there might be no heart sounds, but heart action would continue for about a minute after respiration had ceased. According to Hazard (20), procaine also inhibits conduction along the peripheral nerves when applied locally, and acts on the ganglions and at the nerve endings of the autonomic nervous system to depress or inhibit conduction.

The problem of explaining all of the various actions, namely conduction changes in the nervous system, in the nerves, ganglions, and nerve endings, as well as conduction changes in cardiac muscle and contraction changes in smooth and striated muscle, is an interesting one. All of these changes are reversible. The facts suggest that the mode of action of procaine is in some reversible reaction with the chemical mediators of the nerve impulse and of muscular contraction (20). Among the compounds concerned with these functions are acetylcholine, cholinesterase, creatine phosphate and the potassium ion. Attempts to discover the relation of procaine to these compounds has so far been confusing.

One of the most important things to know about any anesthetic agent is its action on the heart. As has been previously mentioned, early observations by Beck and Mautz (5)

and later by Burstein (8) indicate that procaine administered either topically to the heart or systemically diminished the hyperirritability of the cardiac conducting system, or possibly the myocardium itself, and reverts a shifted pacemaker to the sinus node. Also, diseased hearts apparently are no more than ordinarily sensitive to procaine. The action of procaine on cardiac dysfunction will be discussed more completely in another section of this paper.

The pharmacognostics of any drug require not only knowledge of its source, preparation and dosage, but also a method of determining its presence in tissues and body fluids after administration. The recently aroused interest in the use of procaine hydrochloride intravenously has demonstrated the need for an accurate determination of blood levels of the drug. Graubard et al (16) undertook the investigation of determining the practicability of detecting procaine in the blood stream after known amounts were injected intravenously.

The method for determining procaine hydrochloride in blood is a modification of the procedure used by Bratton and Marshall (16) for the determination of sulfanilamide in body fluids. Upon diazotization the para-amino radical is produced, forming the basis for a colorimetric test. It was also shown that procaine, added to oxalated human blood would not be altered in such a manner that accurate determinations could not be done. Since the recovery of procaine hydrochloride immediately following its addition to blood in vitro was satisfactory, determinations of procaine levels were made in other specimens

of oxalated blood to which known amounts of procaine had been added. Determinations were made immediately, after one hour, and after twenty-four hours storage in the ice box. It was shown that procaine added in vitro was stable on standing in the refrigerator, and that there was no apparent loss.

Typical signs and symptoms observed during administration of intravenous procaine should be listed since procaine follows the pattern of most drugs in that the dose cannot be estimated with certainty, but the effects of toxicity can usually be avoided by careful observation of the patient during the infusion. About five to seven minutes after the start of the infusion, the patient usually describes a sensation of warmth throughout the entire body. "A comfortable, relaxed feeling becomes manifest, accompanied by a generalized sensation of warmth". A flush is sometimes noted over the head, face and neck, except for a marginal circumoral pallor. Soon after the onset of this flugh, the patient notes a dryness of the mouth, sometimes accompanied by a metallic taste, tearing of the eyes, dilatation of the pupils, and light-headedness. Many patients feel comfortably relaxed with the alleviation of the pain. Minor degrees of drowsiness and sleepiness are nearly always evident. Mild dizziness has been a common complaint during the early part of the injection. The depressant action upon the central nervous system is minimal. Most observers state that in the clinical employment of intravenous administration of procaine they strive not to exceed these manifestations.

Likewise, few cases of intolerance with untoward effects to procaine have been reported, as typically exemplified by Graubard et al (15) who states to date, after two thousand administrations, they have noted no cases of procaine sensitivity or any contraindication to the use of this drug.

The toxicity of procaine varies with different animals, and likewise with different patients. Toxicity depends upon personal tolerance to the drug, percentage concentration, amount of detoxification by the tissues, condition of the patient's fluid and electrolytic balance, and pre-operative medication. Richards (22) has shown that vitamin C and glucose also play an important role in procaine tolerance and detoxification. As previously stated, the dose of procaine cannot be estimated with certainty, but the effects of toxicity can usually be avoided. This may be done by taking the patient's history regarding past anesthetic experiences or drug sensitivities; routine tests for sensitiveness in every preliminary preparation by injecting a drop of one per cent procaine solution intradermally. If there is any doubt, after fifteen minutes a drop can also be instilled into an eye because the conjunctival reaction can scarcely be serious if the skin test is at all questionable after this interval. Few instances of hypersensitiveness have been encountered thus far as reported by most observers.

By proper management of the intravenous procaine therapy the toxic effects may be further avoided. The infusion should not be carried on without constant minute by minute supervision

by trained personnel. There is marked variation in the rate of injection which can be tolerated by various individuals. A rate of injection which is too slow may minimize the likelihood of therapeutic benefit from the infusion, while a rapid rate may induce undesirable and perhaps disastrous consequences. It is known that procaine is rapidly hydrolyzed and its toxicity is relatively low. After rapid intravenous administration, however, quick hydrolysis may not be adequate to prevent accumulation of dangerous levels of procaine in the blood and vital tissues. Procaine also diffuses rapidly and in this way tends to develop toxic concentrations. Such symptoms as restlessness, apprehension, tremors, confusion, delirium, and convulsions may develop in quick succession. This early phase of stimulation may be absent or transitory, and may be replaced or followed by sudden failure of the circulation and respiration. The complications of the intravenous injection of procaine are well known and readily recognized. The symptoms are referable either to the central nervous system with muscular twitchings preceding convulsive seizures or coma, or to the circulatory system with signs of collapse with a cold clammy skin and a rapid thready pulse.

Obviously procaine should be used in the lowest effective concentration and in the least total amount compatible with the purpose for which it is intended, and treatment of reactions must be adjusted to the needs of the individual patient. Procaine is a convulsant so caution in regard to employment of concentrated solutions is necessary. 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.

Treatment to counteract procaine toxicity should not be regarded lightly. There should be an immediate interruption of the injection and intravenous administration of a barbiturate. Most reports indicate that pentothal in 2.5 per cent or 5 per cent concentration is always kept in readiness at the time of administration. It is interesting that Barbour and Tovell (4) reported that at the time of publication of their paper, they had not used pentothal to combat a reaction to procaine in the course of its intravenous administration. This record appears to be significant and substantiates their plan to employ procaine in a 0.1 per cent solution of intravenous administration at a rate never exceeding one thousand cubic centimeter in one hour. Further treatment of the procaine toxicity should include the establishment of an efficient respiratory exchange and administration of extra oxygen. The antidote for respiratory symptoms of intoxication is said to be epinephrine, but thus far, no reports were found in the literature of such symptoms being encountered.

In appraising the toxicity of procaine certain properties of the sulfonamides are pertinent. The reduction of the chemotherapeutic effect of sulfonamides in the presence of pus and cell detritus has been explained by their content of para-aminobenzoic acid. This substance supposedly competes with the sulfonamides for the same receptors in the metabolic process of

bacteria, due to the chemical similarity of the structures of para-aminobenzoic acid and the sulfonamides (Wood) (12), or it interferes on the basis of this similarity with certain catalytic processes (Sevang) (12). Procaine, as well as other drugs containing the para-aminobenzoic acid structure, also will inhibit the therapeutic action of sulfonamides. Hence if the physician decides that sulfonamide therapy is necessary for the welfare of the patient, all procaine medication should be discontinued as soon as possible.

Mention has been previously made to the excellent investigations by Richards in which protecting against vitamin C depletion, starvation, and improper electrolyte balance may increase the tolerance to procaine. Richards (22) was impressed with the fact that in experimental work with barbiturates, it had been observed that vitamin C depleted guinea pigs developed a markedly increased sensitivity to pentobarbital (nembutal), indicated by a prolonged sleeping time, while no such change occurred with barbital or pentothal. The former drug, but not the two latter, is subjected to destruction predominantly by the liver. Increased sensitivity of guinea pigs on a vitamin C low diet had also been noticed by Kinsey (22). Further it was demonstrated that fatty changes in the liver which occurred in these animals, were not responsible for the impaired ability of this organ to destroy nembutal, but that vitamin C itself was probably involved in this process.

In view of the above reference to the effect of vitamin C deficiency upon the reaction to certain barbiturates, it was

considered desirable to investigate the effect of this nutritional deficiency upon the toxicity of procaine. The glycogen content of the liver per se is not necessarily an indicator of the degree of sensitivity to procaine. The experiments were carried out on guinea pigs since this species resembles the human in their inability to synthesize vitamin C. Richards (22) points out that even moderate changes in the supply of this vitamin affect the tolerance to procaine, and how general starvation equally lowers resistance. On the other side he gives evidence for the possibility of increasing tolerance to procaine by giving an extra supply of dextrose and vitamin C to animals in a so-called normal nutritional state. In previous studies with barbiturates he considered the possibility of vitamin C being a part of the enzymatic system connected with the destruction of the barbiturates. A similar proposal for the metabolism of procaine may be made as postulated by Richards (22). This assumption has not been fully proved.

If a correlation of these animal experiments with clinical medicine is made, certain practical conclusions can be drawn. It is frequently the weak and malnourished patient, the "poor risk" case, who is subjected to the extensive use of local anesthetics. Often food will be withheld pre-operatively in order to be prepared for the administration of a general anesthetic if it becomes necessary. Thus one could assume that, in dealing with an organism suffering both from a low vitamin C supply and starvation, the administration of vitamin C and dextrose in liberal dosage would fortify the resistance of such

patients to possible central toxic effects to procaine. It must be left to clinical experience to pass on the soundness of these conclusions.

Beck and Mautz (5) in a paper entitled "The Control of the Heart Beat by the Surgeon", published in 1937, stated that one method for the control of reactions produced by surface stimulation to the heart was by the use of procaine or metycaine applied to the surface of the heart. They continued to state that procaine quiets the heart rate very effectively, and that either procaine or metycaine were more effective than potassium chloride without producing the dilated, flabby heart such as results from the use of potassium chloride. They also reported that procaine was efficacious in stopping auricular fibrillation. This observation undoubtedly was a stimulus for other investigators interested in the cardiac arrhythmias to continue the study of procaine as it affected the heart. It naturally followed that interest in the use of the intravenous route as a method of administering the procaine to obtain the desired effect upon the heart was also attempted.

Further interest in this problem of controlling arrhythmias induced by external stimuli resulted from the ever increasing knowledge and techniques of intrathoracic and cardiac surgery. Interventions on or about the heart are becoming increasingly more numerous. Pathologic conditions of the pericardium, of the myocardium, and of the great vessels about the heart are currently explored and corrected. Removal of intracardiac foreign bodies have recently been completed. One of the major

problems incidental to these manipulations is the disturbance produced in cardiac contractions from local mechanical stimuli, so any chance at removal of this barrier to developing further techniques in cardiac surgery immediately creates interest in this problem.

Burstein, Marangoni, DeGraff, and Rovenstine (8) published in 1940 that procaine, and related chemical compounds studied, when administered before epinephrine, would protect against the ventricular fibrillation which may be inaugurated in the dog by injecting small doses of epinephrine (0.01 mgm. per kilo) during cyclopropane anesthesia. They also stated that procaine administered intravenously, when ventricular tachycardia followed the injection of epinephrine, arrested the progression to ventricular fibrillation and recovery to normal occurred after a shifting of the pacemaker to the auricles and finally to the sinus node. The intracardiac injection of procaine was found to be efficient in the treatment of sixty-six per cent of animals having developed ventricular fibrillation following epinephrine injection during cyclopropane anesthesia.

These writers concluded that despite the known toxicity of procaine, its use in the treatment of ventricular fibrillation induced by epinephrine seems logical. It has been shown, Beck and Mautz (5) and Burstein (8), that epinephrine sensitizes the automatic tissue of the heart but procaine reduces this irritability, and increases the threshold for stimuli necessary to produce fibrillation. They emphasized that in view of the greater toxicity of procaine in man this treatment

should be reserved for cases in which no other alternative is present.

Stutzman, Allen and Orth (23) found conflicting results to the above described work of Burstein et al in which it was pointed out that ventricular tachycardia and ventricular fibrillation could be prevented by an injection of the procaine preceding the administration of epinephrine, or when mixed with it for simultaneous injection. In the report by Stutzman et al, they stated that in twenty-seven of several hundred dogs anesthetized with cyclopropane, the injection of epinephrine produced unequivocal ventricular fibrillation. This fibrillation was treated by the intravenous or intracardiac injection of sixteen milligram (whereas Burstein et al employed five milligram) of procaine per kilogram of body weight. Despite the fact that the administration of procaine was completed within a period of less than thirty seconds, not a single instance of fibrillation was altered by this treatment. These writers then concluded that while the use of electrical shock may prove effective in the exposed, fibrillating heart there is no practical method available at the present time for abolishing ventricular fibrillation if it occurs in the intact animal during cyclopropane anesthesia. The injected procaine at the time of fibrillation is not well circulated through the heart and it can therefore hardly be expected to be effective. Even massaging the heart did not improve the results.

Wiggers and Wegria (25) had also reported in 1940 that

observation on fibrillation induced in dogs indicates that procaine raises the fibrillation threshold during the vulnerable period as it does the threshold for premature systoles during diastole. They further stated it was not a preventive. They also stated that revival by countershock occurred promptly, but since this always occurred in normal hearts, no deductions could be drawn regarding the adjuvant action of procaine. Shen, Simon and Van Dongen (17) have demonstrated that procaine inhibits the development of arrhythmias and ventricular fibrillation which may occur upon the injection of epinephrine into cats and rabbits anesthetized with chloroform. Van Dongen has shown also that procaine inhibits the development of both auricular and ventricular fibrillation from electrical stimulation of these chambers in cats and rabbits.

Hirschfelder and Tamcales (17) reported the results of their investigation in 1942 as concerned procaine and related substances on auricular fibrillation in dogs. In five dogs they found that procaine in doses of ten to twenty milligram per kilogram body weight intravenously stopped fibrillation produced by the minimal effective faradic stimulation of the atria, but this resistance to fibrillation passed off rapidly, often within five minutes. Larger doses, forty to eighty milligram per kilogram body weight, prevented even maximal faradic stimulation from producing auricular fibrillation. In four dogs auricular fibrillation induced by dropping five drops of 1:500 solution of acetyl-beta-methyl

choline chloride solution on to the atria was stopped within thirty-five seconds by the intravenous injection of one to six milligram of procaine per kilogram body weight. The effect of the smaller doses of procaine was very transitory because the application of the same stimulus five minutes after cessation of the fibrillation usually caused the fibrillation to reappear.

It has been known that during general anesthesia the cardiac conducting mechanism becomes more sensitive and cardiac arrhythmias may occur. In electrocardiographic tracings performed during surgical anesthesia with all the commonly used general anesthetic agents, Kurtz, Bennett and Shapiro (6) found a surprisingly high incidence of arrhythmias. Thus, every one of six patients to whom chloroform was administered showed some cardiac disturbance. In those given ether, only two out of twenty escaped the development of any arrhythmia. The majority of the cardiac irregularities under either of the above anesthetic agents consisted of a downward displacement of the pacemaker. Of the forty-one patients anesthetized with cyclopropane, some cardiac arrhythmia developed in thirty-three; the most frequent abnormality consisted of extra systoles. With vinyl ether an arrhythmia developed in five out of seven cases. Under avertin, four of five patients had an arrhythmia. Under nitrous oxide, there were electrocardiographic changes in eight of ten patients. During ethylene anesthesia, eight of eleven patients developed cardiac arrhythmias. It is significant to point out that in many cases

the clinical anesthetist was unable to discern any irregularity in the peripheral pulse whereas the electrocardiograph did show some abnormality. Furthermore, in cases in which the irregularities were noted, the recorded pulse rate was from thirty to one hundred points lower than the actual heart rate.

Disturbances in cardiac rhythm during general anesthesia seem to be due to sensitization of the cardiac-conducting mechanism. This increased cardiac irritability during anesthesia is such that certain drugs which have a definite cardiac action have been observed to cause toxic effects when doses which are considered therapeutic in the conscious individual are administered to an anesthetized subject. Certain anesthetic agents such as chloroform, ethyl chloride and cyclopropane are particularly likely to exhibit these effects. Thus, it was observed that ventricular fibrillation could develop during chloroform anesthesia following the injection of a small dose of epinephrine. The same effect was shown to be possible during cyclopropane anesthesia. There are case reports which indicate that even during ether anesthesia the use of epinephrine as a local vasoconstrictor to control bleeding may result in serious complications even to the point of fatal ventricular fibrillation. Cardiac hyperirritability during general anesthesia is also enhanced in conditions which cause excess secretion of the adrenal glands or when there is direct stimulation of adrenergic nerves.

Following the experimental investigations which showed that procaine was effective in the treatment of cardiac

arrhythmias produced by small doses of epinephrine injected into dogs anesthetized with cyclopropane, Burstein (6) recommended the use of procaine hydrochloride to diminish cardiac irritability during general anesthesia. In subsequent clinical applications it was observed that acute arrhythmias during gneral anesthesia could be improved by the intravenous injection of procaine. The initial dose of procaine used at that time was fifty milligram in a one per cent solution injected rapidly intravenously into an adult who had been given a general anesthetic agent. This dose of fifty milligram has been found to be insufficient in many cases as evidenced by the fact that to clear an arrhythmia the initial dose had to be repeated once or twice at five-minute intervals. The initial dose now suggested is one hundred milligram in a one per cent solution. Indeed, the tolerance of the adult patient under general anesthesia to procaine given intravenously has been found to be near one gram (1000 milligram) as exemplified by two reported cases in which one gram of procaine was inadvertently administered intravenously. In one case, five cubic centimeters of a twenty per cent solution had been intended. In the other case, one gram of procaine crystals was introduced into five hundred cubic centimeters of blood in a conically shaped flask. In both of these cases the patients exhibited some transient muscular twitchings. These effects of stimulation of the central nervous system were transitory but illustrate that large doses of procaine may overcome the depressive effects of general anesthesia. A dose of one

hundred milligram of procaine may then be considered one-tenth the tolerance dose and is deemed safe when the surgical stage of anesthesia supervenes.

Burstein while 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 intravenously. The opportunities afforded anesthetists, serving on thoracic surgical teams to administer procaine in one per cent concentration for the treatment of cardiovascular emergencies occurring during major intra-thoracic surgical procedures yielded valuable information, and further served to substantiate Burstein's and Marangoni's original concepts. That is, the objective of the therapy is to decrease irritability of the cardiac conduction mechanism in the presence of cardiac dysfunction associated with anesthetic and surgical procedures.

It has since been advocated by Tovell (4) that if procaine hydrochloride in one 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%) administered slowly (one gram in one hour) as a prophylactic measure, immediately before and during operative procedures involving intrathoracic structures likely to produce these untoward cardiac effects, is well advised.

A direct outgrowth of the prophylactic use of solutions

of procaine in weak concentration, prior to and during intra-thoracic 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 (0.1% 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. Barbour and Tovell (4) state it is their belief that this therapy was instrumental in rendering these patients operative and their postoperative courses uneventful.

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 one-tenth per cent concentration to reduce futile activity associated with excess irritability, is warranted as a prophylactic measure.

Long, Oppenheimer, Wester, and Durant (20) recorded the following electrocardiographic changes with increasing doses of

intravenous procaine: usually a heightening, sometimes a flattening or even an inversion of the T wave; a lowering of the voltage of R, an increase in the depth of the S wave and the formation of a "J", a depression of the S-T segment; an increase in the width of the QRS complex; a prolongation of the P-R interval; ventricular tachycardia, and ultimately, ventricular fibrillation. The changes in the S and S-T segment were not always seen in lead II, although they were usually present in the precordial leads. Such changes in the electrocardiograph apparently indicate changes in the repolarization of the ventricular musculature, changes in the rate of conduction of the cardiac impulse through the bundle of His and the ventricular muscle, and to a lesser extent changes in the rate of conduction through the A-V node and perhaps through the atrial musculature. The most pronounced of these changes is in the conduction through the bundle of His and the ventricular musculature resulting in bundle branch block.

The lowering of the blood pressure and more particularly the pulse pressure as the QRS complex widens, together with the increasingly weak second heart sound, suggests that there is a loss of tonus and a weakening of the force of the heart beat in addition to the change in conduction. Procaine lowers blood pressure in the heart-lung preparation. A part of the fall in blood pressure is probably due to the vasodilatation which occurs with procaine, but vasodilatation alone with no change in the cardiac output should not lower the pulse pressure. The greatly dilated heart at necropsy and the flabby condition

of the muscle also speak for the effect of procaine on the cardiac musculature. In support of this view is the fact that Hazard (20) reported that procaine decreases the tonus of both striated and smooth muscle and in large doses causes complete muscular paralysis.

Many of the reported experiments relating to treatment of cardiac conditions have been performed on experimental animals, and cardiologists have apparently approached with trepidation the use of procaine intravenously in heart disease. Uhley and Wilburne (24) in 1948 reported changes in the electrocardiograph of dogs to which procaine had been administered by rapid intravenous injection. These workers found procaine, in the dosages used, to be a powerful depressant of conduction within the heart, and reported prolongation of the PR and QRS intervals and alterations in the configurations of all the various complexes of the electrocardiogram. They record their conviction that these experiments demonstrate the potential hazards of procaine, and include in their discussion a supposition that diseased hearts might tolerate only fractions of customary dosages of procaine.

Doak and Selke (10) reviewed the investigation of Uhley and Wilburne and concluded that the report of the latter group might easily lead one to regard the intravenous administration of procaine as a procedure fraught with menace to the heart. Doak and Selke further concluded that with a more deliberate consideration of their methods and findings, along with a review of the references cited in their paper, one is lead to a much

greater sense of security in the use of the usually recommended manner of treatment.

Most of the writers in the English and American literature who have advocated the use of procaine intravenously have suggested the use of one gram of the drug for the average patient, to be administered by slow intravenous drip, with a volume of solution between five hundred and one thousand cubic centimeters. It has been previously emphasized in this paper that a slow rate of administration and constant observation of the patient were imperative. The amount of procaine remaining in the body after an intravenous injection varies directly with the rate of injection and inversely with the elapsed time, hence it seems reasonable to assume that when one gram of procaine hydrochloride is administered slowly by intravenous drip to a human being there is never more than a small fraction of this amount of procaine existing as such within the person's body.

The dogs used in the experiments of Uhley and Wilburne were given fifty milligram of procaine hydrochloride per kilogram of body weight, a dose which is roughly equivalent to two and one-half to five grams for the human being. The drug was administered in five per cent solution, the injection being completed within fifteen to one hundred and twenty seconds. The dogs were anesthetized with pentobarbital sodium to prevent the development of generalized convulsions, which otherwise would probably have followed.

Doak and Selke (10), in an effort to determine the apparent effect of procaine given intravenously in the usually recommended

manner upon the presumably healthy human heart, made electrocardiographic tracings of a group of patients, each of whom had already been selected for intravenous procaine therapy of some fibrositic or rheumatic disorder. These patients had been selected for treatment without any particular consideration having been given to their cardiac status. In each case one gram or less of procaine hydrochloride was administered by intravenous drip in 0.1 per cent concentration in physiological saline solution. The total time for the injection varied between one and three hours and the entire procedure was carried out under the constant close supervision of trained personnel. One of these patients reported no subjective sensations during the infusion, while others reported dizziness, numbness of the face, a sensation of thickening of the tongue, dryness of the mouth, nausea or a sense of unreality. The onset of any very definite subjective sensation of this sort was taken as an indication for slowing the rate of injection. Slowing or stopping the injection relieved the abnormal sensation in a few seconds in each instance. Electrocardiographic tracings were made on each patient immediately before the injection was begun and shortly before the termination of the injection when the effect was presumably at its height. Each tracing included the three standard leads, the three augmented unipolar extremity leads, and the precordial leads V2, V4, and V6.

Each of these patients was suffering from a marked somatic discomfort and consequently the tracings showed more of the effects of somatic muscle spasm and voluntary muscle movement

than is ordinarily seen in electrocardiograms. These artifacts were taken into account in the interpretation of the tracings, and those segments of the electrocardiograph which seemed most nearly to demonstrate the true state of affairs were selected for representation. As previously stated, the cases were selected for treatment without any particular attention being paid to the cardiac status. It seems from the information available that five of the six patients might be expected to have hearts with less than normal reserve strength. In five of the six cases the rate of injection of procaine was such that definite subjective symptoms ensued, and the second electrocardiograph was made as nearly as possible at the time these subjective symptoms were present.

When changes appeared in the electrocardiograms which might be ascribed to the infusion of procaine, these changes were largely of the same type; and though extremely mild, suggested the pattern observed by Uhley and Wilburne following the rapid intravenous injection of toxic doses of procaine into animals. There was slight slowing of heart rate which might well have been due to the period of bed rest and the general relaxation induced by the drug. There was occasional prolongation of the PR interval, the QRS duration, and the QT duration which was not beyond what might have been observed in simple slowing of the pulse rate. Since these various prolongations have been observed in exaggerated form following the employment of toxic doses, however, they must be regarded here as being due to the drug. Slight diminution in

the amplitude of the various complexes was usually noted in the standard leads and the unipolar limb leads, and probably represents a consistent effect of the intravenous infusion of procaine. It was only in the precordial leads, however, that any suggestion of significant change in configuration of the complexes was ever observed, and it must be remembered that in these leads a slight change in the position of the heart within the thorax can materially affect the configuration of the electrocardiogram. It is seen also that occasionally the amplitude of the complexes in the precordial leads taken in the fifth and sixth positions may be slightly increased while the amplitude of the complexes in the other leads is slightly diminished.

It certainly cannot be held that absence of significant changes in the electrocardiograph following the exhibition of a drug establishes the fact that the drug is innocuous. However, it is felt that this study by Doak and Selke demonstrates the relative safety, from the cardiological standpoint, with which the therapeutic effectiveness of intravenous injections of procaine may be explored. The results of the injection of toxic amounts of the drug into animals illustrate the consequences of over dosage or of the use of the drug in the hypersensitive individual. There is no obvious reason to suspect that diseased hearts are more than ordinarily sensitive to procaine. An irritable heart, exhibiting arrhythmia or ectopic beats, might well be expected to show an unusual resistance to the depressing effects of the drug.

In summary, certain considerations as apply to the general employment of intravenous procaine should be reviewed. Certainly additional investigative work is necessary, but sufficient clinical trial has already been undertaken to warrant the use of intravenous procaine in clinical practice. Present concepts dictate that procaine is employable only in those regions in which an inflammatory response has occurred with attendant increased capillary permeability. The procaine administered with large quantities of fluid then transudes into the tissue areas in which anesthesia is desired, and the sensory afferent impulses which would be manifested as pain are "blocked" with subsequent relief to the patient. Hence, intravenous procaine may be therapeutically employed in inflammatory and traumatic conditions to include post-operative control of pain and, though it does not supplant opiate sedation, the dosage and frequency of opiate administration is reduced.

Intravenous procaine is also now employed pre-operatively today to achieve that which Lundy (12) has described as balanced anesthesia. This term connotes additive anesthesia, in which no single agent is depended upon to maintain a maximum effect, but rather the goal of maintaining anesthesia without undue danger to the cardiac, respiratory or circulatory systems of the patient is accomplished by administration of a multiplicity of drugs. Of course the agents must be compatible or synergestic. In an attempt to attain the above mentioned balanced anesthesia, a decreased toxicity of the procaine was observed (13) by the addition of either one-half gram or one

gram of pentothal to the procaine solution. As has been previously emphasized, constant observation of the patient during the intravenous procaine infusion is necessary because of the respect, not fear, of the toxic reactions possible with procaine administration. The range of usefulness of intravenous procaine may be further widened as its toxic reactions are further reduced, not only by the employment of pentothal, but with other additive agents. In discussing the avoidance of toxic reactions, mention should again be made of Richard's investigation and recommendation that vitamin C depletion, starvation and improper electrolytic balance should not be overlooked.

A very important contribution in the use of intravenous procaine originated with the work of Beck and Mautz and later Burstein in which they reported that intravenous procaine would reduce hyperirritability of the cardiac conducting system, and revert a shifted pacemaker to the sinus node. The rationale for the use of procaine to combat cardiac hyperirritability derives from this experimental work. It is believed by the writer that the most significant and beneficial use of intravenous procaine as pertains to its action on the heart is its use as a prophylactic measure. It is advised as a prophylactic measure not only before and during operative procedures involving intrathoracic structures likely to produce untoward cardiac effects, but also to minimize the state of cardiac hyperirritability produced by general anesthesia. By the employment of intravenous procaine pre-operatively and

during the operative procedure the incidence and severity of cardiac arrhythmias which are so frequent during clinical surgical anesthesia may be diminished.

Of greatest significance, in reviewing observations of intravenous procaine therapy up to the present time, is the enthusiasm with which most investigators have reviewed their results in clinical application of this procedure, as well as the attitude that there are many significant facts, that, if properly interpreted, can contribute to the more scientific use of intravenous procaine or its congeners.

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