NEUROPHARMACOLOGY OF PROCAINE.* † ‡ § I. PERIPHERAL NERVOUS ACTIONS

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It has been difficult to explain the occasional beneficial results in chronic pain syndromes from the intravenous administration of a dilute solution of procaine. Several lines of evidence basic to an understanding of this fact would seem contradictory or restrictive. First, there is chemical evidence that procaine undergoes rapid hydrolysis in blood and liver to DEAE (diethylaminoethanol) and PABA (paraaminobenzoic acid), so that the clinical procaine unit of 4 mg. per kilogram is imperceptible in serum within minutes following the completion of injection (1, 2). Similarly, the results of present experiments have shown that the pharmacologic actions of procaine, as measured in the laboratory animal, are of short duration. Rapid enzymatic destruction of procaine and measurably short drug actions would seem paradoxical at first with long-lasting relief from pain following dilute infusions of procaine. Secondly, the popular theories of procaine action which stress a peripheral effect upon receptors, peripheral neurons and autonomic ganglia (3, 4) would seem insecure and in need of amplification for the following reasons:

1. Procaine dose-response curves for peripheral nervous elements indicate that a simple dilution factor may operate against the effective concentration of procaine at the periphery following the intravenous administration of dilute solutions (5).

2. The attractive hypothesis of a changed capillary permeability following trauma, which would allow for a selectively high concentration of procaine at the site of injury (6), will not explain all the results, nor is there good documentation for it.

3. There is wide clinical experience with the use of dilute intravenous procaine infusions for chronic pain syndromes (3, 7–12) where it would seem necessary to invoke central pain mechanisms in explaining the "vicious-cycle" of pain that has developed (13, 14). In many of these instances, a zone of tissue damage or increased capillary permeability cannot be demonstrated or is not likely to exist.

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It would appear that the site of procaine action cannot be at the periphery alone. In the light of modern neurophysiologic theory of pain mechanisms (13, 15), the apparent conflict might be resolved if there were evidence of central procaine actions. Experimental demonstration of procaine effects upon multineuronal circuits, such as exist in the central brain-stem reticular formation and the interneuronal systems of the cortex (16), would help rationalize the clinical results. With such evidence, it is conceivable that a long-lasting reorganization of central nervous system functions might result from single dilute infusions of procaine, although, in animals, the measurable pharmacologic actions following each infusion are transient and reversible.

The present study has explored some of these possibilities. A correlative study of the neuropharmacology of procaine administered intravenously has been made. The design of experiments has included the testing of a mosaic of neuronal actions at several functional levels in the nervous system. Strict quantitative analysis of the present experiments has not been possible, but the findings establish the fact of a differential vulnerability to procaine of various functional units in the nervous system. The data from these studies have implications which aid in validating a concept of central procaine action as it relates to the clinical problem of pain. The results of these experiments will be presented in two papers, of which this is the first.

**Experimental Methods**

In the two studies which will be reported, acute experiments were carried out on 26 dogs, 38 cats, and 4 rabbits. Ten experiments were performed using trained dogs with Thiry-Vella intestinal loops. One patient with a hypersensitive carotid sinus reflex, and one with a femoral arteriovenous fistula caused by high-velocity missile injury, were available for study.

**Autonomic Neuro-effector Transmission.** The general pharmacodynamic actions of procaine administered intravenously were studied using intact, one-vagus and vagotomized animals. Healthy unselected stock dogs and cats under ether, intravenous nembutal®, or intraperitoneal dial®-urethane anesthesia were used. Femoral artery or carotid artery blood pressure was recorded on smoked paper, using a mercury manometer; or a metallic bellows ink-writing recorder system was used. In some experiments regional heparinization of the cannulated vessels was accomplished so as to minimize intracannular clotting. Respiratory tracings were obtained using an air-tambour recording system attached to a pneumograph or to an intrapleural cannula.

The effects of intravenous injections of procaine upon the cardiac vagus were studied using a 100 per second bradycardia or asystole-producing stimulus to the intact vagosympathetic trunk. In some experiments, glass-shielded electrodes were applied to the peripheral end of the cervically sectioned nerve trunk. Heart rate, blood pressure,
and respiratory responses to the intravenous administration of acetylcholine and epinephrine were recorded before and after procaine injection in the intact, vagotomized, dibenamine®-treated or atropinized animal.

Neuro-effector Transmission to Skeletal Muscle. The effects of close arterial injections of procaine (ipsilateral femoral artery) as well as the response to intravenous administration (contralateral femoral vein) were studied in the nerve-muscle preparation (peroneal-tibialis anticus or sciatic-gastrocnemius), using intact dogs under light nembutal anesthesia, dogs made acutely spinal at a high cervical region under ether and maintained with artificial respiration, and cats anesthetized with nembutal given intravenously or intraperitoneal dial-urethane solution. Relatively isometric contractions of the indicator muscle were recorded using a smoked drum and a Meyerhof-type myograph. In some experiments, parallel insulated bipolar copper-recording electrodes, the tips separated from 5 to 10 mm., were inserted into the muscle mass and connected through an amplifier-recording system to a Grass ink-writing electro-encephalograph. Using an electronic stimulator, single supramaximal shocks, usually five times the minimal voltage required to elicit a maximal twitch response, were delivered every two seconds through glass-shielded platinum electrodes applied to the peripheral end of the sectioned peroneal or sciatic nerve.

Synaptic Transmission in Autonomic Ganglia. A variety of testing procedures was used to evaluate cardiovascular reflex responses which are mediated through autonomic ganglia (17, 18). Under similar conditions, a series of testing procedures were carried out before and after the intravenous administration of procaine, and a comparison study was then made. The same testing procedures were repeated after ganglionic-blockade had been achieved by a 5 to 10 mg. per kilogram dose of TEAC (tetra-ethylammonium chloride). Sufficient time was allowed to elapse between the injections of the different drugs for metabolic disposition of the first (as evidenced by the integrity of the testing reflexes) before injection of the second solution. The testing procedures utilized included the following:

1. Base-line changes in blood pressure and heart rate in the nembutalized animal following ganglionic-blockade provide an estimate of the level of sympathetic tone to heart and blood vessels (17, 18).

2. The pressor response to bilateral carotid artery occlusion (17), the cardiovascular over-shoot which follows forced obstructed expiration (19), and the pressor response with cardio-acceleration which result from intravenous acetylcholine (20), can be interpreted in relation to the general level of responsiveness in postganglionic cells at autonomic ganglia, the liberation of epinephrine from the adrenal medulla, and the intactness of sympathetic outflow.

3. Stimulation of the central end of the cervical vagosympathetic trunk elicits reflex responses of heart rate and blood pressure in suit-
able preparations if ganglionic transmission and peripheral neuro-effector mechanisms are intact. Protrusion of the eye, retraction of the nictitating membrane, and pupillary dilatation following stimulation indicate an intact ganglionic and terminal neuro-effector system for these structures. Additional information can be obtained from the observation of nictitating membrane and pupillary responses to intracarotid injection of various autonomic drugs.

4. The intravenous injection of adrenaline tests the responsiveness of arteriolar smooth muscle, as well as the reflex cardio-decelerator and respiratory-inhibiting mechanisms activated by the pressor response elicited.

5. Respiratory alterations and blood pressure responses to intracarotid injections of acetylcholine and nicotine in atropinized animals are susceptible to analysis in terms of carotid body respiratory reflexes and direct excitability of cells in the postganglionic autonomic neuronal system (21).

Testing procedures of this type were carried out in anesthetized animals under the experimental conditions described under Autonomic Neuro-Effector Transmission.

In addition, two unanesthetized dogs with Thiry-Vella loops were available for a comparison study of the effects of procaine, TEAC and mephenesin (Myanesin®-a:b-dihydroxy-g-(2-methylphenoxy)propane) upon the minimal intraluminal pressure required to elicit the intestino-intestinal inhibitory reflex (22). Information concerning the functional integrity of reflex arc conduction in unanesthetized man was obtained from a study of two patients: (1) A 45 year old male with a femoral arteriovenous fistula, and (2) A 74 year old man with advanced arteriosclerosis who demonstrated a hypersensitive carotid sinus reflex. In the first instance, cardiac slowing was reflexly produced by the manual occlusion of the arteriovenous communication; in the second subject, the same reflex response was effected by vigorous massage over one or both carotid sinus areas. The effect of intravenous procaine injection upon this reflex cardiac response was tested; then a comparative study using TEAC to produce ganglionic-blockade was made.

Receptor Mechanisms. Alterations in the threshold to specific modalities of cutaneous sense following the intravenous administration of procaine were not tested. Evidence was obtained which relates to the chemo-receptors of the carotid bodies and the aortic arch. A study of the hyperpneic response to intracarotid injection of nicotine and acetylcholine was made in atropinized animals (23). Procaine effects upon the carotid-aortic pressoreceptor mechanism were judged from the cardiovascular responses to alterations of intracarotid pressure, as well as from clinical studies described under Synaptic Transmission in Autonomic Ganglia. Respiratory responses following vagus nerve stimulation and vagus nerve section, as modified by intravenous
procaine administration, provide some information as to vagus nerve conduction and the pulmonary stretch receptors.

Conductivity of Peripheral Nerves. Isolated peripheral nerve conduction studies were not done but were tested by indirection in many of the experiments which have been described. An intact reflex arc in the anesthetized preparation or unanesthetized man would suggest the functional adequacy, at least, if not the completeness of afferent and efferent nerve conduction, synaptic transmission, and receptors and effector organs.

Intravascular Procaine Injections. A fresh solution of procaine in isotonic saline solution was prepared for each experiment. One hundred cc. stock bottles (N-591: 1 per cent novocaine®) 30 cc. bottles (N-190), or 5 cc. sterile ampuls (N-220) were used. Procaine concentrations from 1 to 20 mg. per cubic centimeter were injected into a peripheral artery or vein at different rates of administration. The stock solutions used are reported by the manufacturer to contain small amounts of substances other than procaine; for example, each cubic centimeter of the 1 per cent novocaine solution contains the following: novocaine, 20 mg./cc., sodium chloride 3.5 mg., sodium bisulfate not more than 2 mg. per ampul, and chlorobutanol, 0.25 per cent.

Results

Autonomic Neuro-effector Transmission. In the intact animal, the slow intravenous injection of procaine 1 to 5 mg. per kilogram failed to exert significant effects upon the blood pressure, heart rate or respiration. The clinical procaine unit of 4 mg. per kilogram in unanesthetized man, injected over a twenty minute period, is usually without significant effect upon these measurements. Intravenous procaine dosages in animals of from 10 to 25 mg. per kilogram produced slight alterations in baseline cardiovascular and respiratory measurements when slow rates of injection were used. The rapid administration of large doses of procaine resulted in a fall in blood pressure which was roughly proportional to the rate of administration. The depressor response in such instances was usually associated with a slight bradycardia. These effects were not significantly altered by prior vagus section or atropinization. Intravenous doses of procaine 5 to 20 mg. per kilogram failed to prevent epinephrine-induced tachycardia. The pressor response to adrenalin did not appear to be altered in these experiments. Adrenalin reversal was not observed, nor was the pressor response to epinephrine increased or prolonged, as occurs following the prior administration of a ganglionic-blocking agent such as TEAC or hexamethonium. Reflex adjustments to the imposition of stress upon the experimental preparation, such as result from forced obstructed expiration, bilateral carotid artery occlusion, or acetylcholine hypotension from the rapid intravenous injection of this substance in large dosages, failed to unmask a procaine blockade.
The minimal alterations which occur in cardiovascular measurements following procaine injection, and the failure of procaine to potentiate the pressor response to adrenalin or to influence the reflex effects of stressful conditions which activate sympathetic vasoconstrictor mechanisms, suggest that under the conditions of these experiments: (1) rapid cardiovascular adjustments are made for any loss of adrenergic tone that may occur following procaine infusion, and (2) reflex homeostatic mechanisms which utilize excitatory adrenergic effector systems are functionally intact following intravenous injections of procaine through a dose range of from 1 to 20 mg. per kilogram of body weight.

Inhibitory adrenergic effector systems did not appear to be blocked by intravenous procaine dosages as large as 20 mg. per kilogram. Evidence for this conclusion is as follows: (1) Adrenergic vasodilatation occurred in dibenamine-treated animals in response to epinephrine injection following prior injections of procaine; (2) adrenergic vasodilatation occurred in the atropinized dibenamine-treated animal in response to nicotine injection, although procaine infusions had been given previously; (3) inhibition of intestinal motility following adrenalin injection in the unanesthetized dog with a Thiry-Vella loop was unaffected by the prior administration of procaine; and (4) the intestino-intestinal inhibitory reflex was functionally intact following dosages of procaine of 5 and 10 mg. per kilogram. A transient but relatively ineffective and variably occurring block of this testing reflex occurred following 20 mg. per kilogram of procaine. This result does not constitute clear evidence for adrenergic blockade by procaine infusions. Observation of a reflex block is in itself no indication of the specific point, or points, in the reflex are at which the drug effect is being exerted. Procaine has been shown to antagonize both vasconstrictor and vasodilator responses to epinephrine in the perfused rabbit ear (24), as well as the vascular responses to histamine and acetylcholine. Adrenergic blockade under these conditions would seem to have occurred at procaine concentrations which are considered as adequate to suppress the over-all activity of effector cells (5).

In summarization of these experiments, no evidence was obtained which could be interpreted as showing adrenergic blockade following intravenous procaine injections through a dose range from 1 to 20 mg. per kilogram of body weight.

Anti-acetylcholine Action. When procaine is injected in pharmacologic doses, its anti-acetylcholine action is readily demonstrable. Less than 5 mg./kg. procaine failed to block the cardiac effects of vagus nerve stimulation in anesthetized animals. Increasingly large dosages of procaine abolished completely the cardiac slowing or asystole which occurs in response to electrical stimulation of the vagus nerve. For example, 15 mg./kg. procaine in an etherized dog weighing 20 kilograms (7-12-48) produced cardiac vagus block for thirty-five minutes. The
protection against an asystole-producing stimulus was complete, at first, and comparable to the results from full dosage atropinization. The functional integrity of vagal afferent axons at this time was indicated by the unaltered respiratory effects of stimulation. The anti-acetylcholine action of procaine outlasts the depressor response and the bradycardia which follow intravenous injection of large procaine dosages.

The duration of cardiac vagus block and neuromuscular blockade seemed to be of comparable degree. Neostigmine antagonism of the cardiac vagus effect of procaine injection could be demonstrated, and cardiac slowing which follows the rapid injection of intravenous acetylcholine was reduced appreciably by the prior injection of procaine. This evidence suggests that the procaine effect is a competitive terminal cardiac vagus block, rather than neuronal or ganglionic blockade.

**Depressor Response.** The intimate nature of the vasodepressor response to the rapid intravenous administration of large doses of procaine was not studied. Leriche postulated a direct procaine effect upon the arteriole with widespread peripheral vasodilatation (10). Normal reactivity to epinephrine and DMPP, a ganglionic-stimulating agent, and failure to block the depressor effect of procaine in plane III etherized dogs by ninth or tenth cranial nerve section, led Haggart and Woods to conclude that the hypotension is of central origin (25).

**Bradycardia.** Although not prominent, the bradycardia following large dosages of procaine injected intravenously is a consistent result. Beyer and Latven (26) observed that 4 mg. procaine per kilogram in the unanesthetized animal exerted little or no influence upon the electrocardiogram. Increasingly large dosages of procaine led to an increased amplitude of the T-wave, a decreased P–R interval, and a decreased R- potential. In our acute experiments, a protective action of intravenous procaine against epinephrine-induced and nicotine-induced arrhythmias was regularly seen in both the intact and the vagotomized animals.

Figure 1 shows the effect of 2 mg./kg. of procaine upon spontaneous cardiac arrhythmias which developed in an etherized animal premedicated with morphine. Results such as these, and our inability to demonstrate adrenergic blockade following procaine administration, suggest that the bradycardia is most likely explainable in terms of direct myocardial depression. A central depressant effect upon cardioaccelerator influences traveling via sympathetic pathways to the heart is not excluded by any of these results. Procaine effects upon the completely denervated heart preparation were not studied.

**Respiratory Effects.** There was little or no change in the rate or amplitude of respiration in the intact animal following the slow intravenous injection of 1 to 5 mg. of procaine. Inspiratory apnea from faradic stimulation of vagal afferents was not blocked by 20 mg./
kg. of procaine. The hypotensive action of intravenous procaine administration in etherized and barbiturate anesthetized animals was associated with little or no respiratory depression if the vagus nerves were intact. In some instances, a depressor response to large dosages of procaine was accompanied by a tachypnea. The synchronous effect upon blood pressure and respiration is best explained in terms of reflex activation of carotid sinuses and aortic arch mechanisms in response to a sudden drug-induced hypotension. Vagotomized animals under moderate to deep ether anesthesia responded to procaine dosages of from

![Graphs showing blood pressure changes](https://via.placeholder.com/150)

**Fig. 1.** Procaine protection against spontaneous cardiac arrhythmias. An 11 kg. dog, morphine 0.015 Gm., light ether anesthesia, femoral artery blood pressure: (A) Before injection of procaine, (B) immediately following 2 mg. per kg. of procaine intravenously, and (C) six minutes after completion of the injection.

10 to 30 mg. per kilogram with a severe decrease in blood pressure and progressive respiratory failure. For example, in one experiment (8, 12, 48) a 30 mg. dose of procaine resulted in a decrease in blood pressure to imperceptible levels with ventilatory failure. Spontaneous resumption of the ventilatory effort occurred only after six minutes of artificial respiration. Procaine in single or cumulative dosages of 50 to 100 mg. usually led to the death of intact, lightly anesthetized cats by ventilatory failure unless artificial respiration was provided.
In a few experiments evidence was obtained that the respiratory center was electrically excitable at the time spontaneous respirations had ceased. Continued procaine infusion led to final electrical inexcitability of the respiratory center, at a time when cardiovascular action was still strong and the heart beat was regular. Prior to the failure of respiration, it is likely that the curariform action of procaine (see below) contributes to the total picture of ventilatory failure which occurs.

**Neuro-effector Transmission to Skeletal Muscle.** Traditional criteria of a curare-like action are: (1) muscle response to motor nerve excitation is abolished, (2) nerve conduction is unimpaired, (3) direct excitation of muscle by electrical stimulation is still possible, and (4) release of the chemical mediator continues during the blockade. A curare-like action of procaine following intra-arterial injection was demonstrated first by Harvey (27). As might be expected, larger dosages of procaine are required to elicit this effect when the intravenous route is used. In one of the more sensitive preparations (1, 16, 49), 2.5 mg./kg. of procaine by arterial injection reduced the amplitude of the neuromuscular response by 60 per cent. Repetition of the procaine dosage in this nembutalized dog increased the depression of the response to an 80 per cent reduction in amplitude. Successive doses of procaine of 2 mg./kg. given intravenously to this animal were ineffective until a cumulative dosage of 10 mg. had been achieved. A typical record from another experiment, showing the curare-like action of procaine, is shown in figure 2. The decrease in the twitch response is prompt, the effect is of short duration, and incomplete recovery of tension can be obtained by nerve tetanization. The *anti-procaine action of epinephrine* is also illustrated in figure 2. It would appear to...

![Figure 2](image-url)
be similar in all respects to the anti-curare action of epinephrine which was described by Rosenblueth, Lindsley and Morison (28).

The prompt induction of neuromuscular blockade, the lability of the response, and its sharp antagonism by epinephrine suggest that the procaine effect is curare-like. A striking similarity between the chemical structure of acetylcholine and procaine has been noted. On this basis, in a discussion of the local anesthetics, Thimann (29) suggested that the procaine blockade of neuro-effector transmission would seem to exemplify the principle of biologic competition for a substrate by virtue of structural imitation. Harvey demonstrated that procaine reduces the contraction evoked by acetylcholine and eserine potentiation as well, but exerted no influence upon KCl contraction of skeletal muscle. Fulton (30) observed that 5 per cent novocain applied to the sciatic-gastrocnemius nerve-muscle preparation failed to influence peripheral nerve conduction or muscular contractility. The anti-curare action of epinephrine is an immediate effect, dissimilar to the anti-curare effect of the cholinesterase drugs and in sharp contrast to the depolarization response that is produced by the methonium compounds (31, 32).

The theory of competitive inhibition in explanation of procaine neuromuscular blockade is simple and reasonably acceptable, but alternative possibilities do exist. There are the added possibilities of: (1) transmitter failure due to the immobilization of a chemical mediator, (2) impaired production of the transmitter, (3) and a normal end-plate response but direct depression of the muscle itself. Rapp (33) studied the inhibition of creatine phosphate and acetylcholine breakdown in frog sciatic nerve extracts which occurs following the addition of procaine. He suggested that neuromuscular blockade might occur by a metabolic block which prevents energy release in the apparently essential reaction between acetylcholine and energy-rich creatine phosphate. Extending the studies of Sherif (34), Watts' investigation of the in vitro action of the local anesthetic agents upon the respiration of brain nerve tissue indicated that a blockade of the enzymatic chain is occurring at the cytochrome c-cytochrome oxidase level, or at some factor necessary for the reduction of cytochrome (35). The early studies of Harvey (27) revealed a depression of acetylcholine synthesis in the superior cervical ganglion of the procaine perfused cat. Gesler and Matsuba (36) observed a depression of directly stimulated denervated tibialis anticus muscle in the dog following the intra-arterial administration of procaine. Feng (37) noted the continued effectiveness of nerve impulses in setting up relatively large and prolonged end-plate potentials during procaine neuromuscular blockade. The implication of these latter studies is that the blockade is related, at least in part, to an increased threshold for effector cells.

Synaptic Transmission in Autonomic Ganglia. The classical studies of Harvey in 1939 demonstrated ganglionic blockade following pro-
caine perfusion of superior cervical ganglia in the cat (27). It has not been possible to demonstrate autonomic blockade following procaine dosages of 5 mg./kg. or less using a 5 to 10 mg. ganglionic-blocking dose of TEAC for comparison studies. Partial blocking actions could be shown following the intravenous administration of large doses of procaine in the order of 20 to 100 mg. per kilogram. A variety of testing methods was used. Similarly, reflex arc studies in unanesthetized animals and human subjects failed to provide evidence of autonomic blockade following intravenous procaine infusions. These data may be summarized as follows:

**Pressor Response to Increased Intrapulmonic Pressure.** Sarnoff, Hardenbergh and Whittenberger (19) have shown that the characteristic and consistent pattern of arterial pressure change resulting from a thirty second alteration of intrapulmonic pressure could be abolished by an autonomic ganglionic blockade. Intravenous procaine injections in 5, 10 and 20 mg./kg. doses were ineffective in this respect. No contrary data were obtained in 5 experiments.

**Cardio-Accelerator Response and Pressure Over-Shoot Following Acetylcholine Hypotension.** The post-injection response has been shown to be due to the reflex activation of adrenergic nerves as well as epinephrine liberation from the adrenal medulla (20). Ganglionic blockade was provided by the prior administration of TEAC. The ineffectiveness of procaine in blocking these reflex activities following the intravenous injection of acetylcholine was demonstrated.

**Pressor Response to Bilateral Carotid Artery Occlusion.** The pressor response may be eliminated by sympathetic ganglionic blockade (17, 18, 21). Procaine dosages to 20 mg./kg. were uniformly ineffective in abolishing such responses.

**Pressor Response to Nicotine and Acetylcholine in Atropinized Animals.** A pressor response may be produced by the activation of vasoconstrictors through intravenous or intra-carotid injection of nicotine or acetylcholine in the atropinized animal. These drug effects are blocked by the prior administration of TEAC, little if any influenced by large procaine dosages.

**Intra-Carotid Injections, Centripetal Stimulation of Vagosympathetic Trunk.** A 15 mg./kg. dose of procaine injected intra-carotid (10, 12, 48) failed to block ipsilateral pupillary dilatation from centripetal stimulation of the vago-sympathetic trunk, acetylcholine injection, or the intra-carotid injection of adrenalin. Protrusion of the eye, retraction of the nictitating membrane, and pupillary dilatation following nerve stimulation suggest the integrity of preganglionic neuronal conduction, ganglionic transmission, and terminal neurohumoral mechanisms. Central vagosympathetic trunk stimulation produced in some animals a reflex pressor response while complete cardiac vagus block was operative.
Reflex Arc Studies in Unanesthetized Animals and Man. Ten experiments involving more than sixty distending pressures and reflex responses in 2 dogs with Thiry-Vella loops gave consistent results. In 3 experiments, 20 mg./kg. of procaine resulted in a ten to twenty second inhibition of rhythmic contractions in the indicator jejunal segment without alteration of tonus. A block of the intestino-intestinal inhibitory reflex following procaine injection was of less than five minutes duration. A 5 to 10 beat per minute increase in heart rate occurred with the procaine injections. Smaller dosages of procaine were without effect upon rhythmic contractions, intestinal tonus, or the integrity of the intestino-intestinal inhibitory reflex. TEAC in 4 mg./kg. dosage produced a significant decrease in tonus and a five minute period of complete inhibition of rhythmic contractions. The intestino-intestinal reflex was found to be intact following the recovery of intestinal motility in the indicator segment. A 70 mg./kg. dose of mephenesin did not alter intestinal tonus, rhythmic contractions, or the intestinal inhibitory reflex.

Clinical studies were made on two patients:

Case 1. L. S. (E–20–366), a 43 year old male weighing 65 kilograms with a right femoral arteriovenous fistula incident to a high velocity missile injury, demonstrated a pronounced reflex bradycardia upon manual compression and closure of the fistula. Increased peripheral resistance and an elevated mean arterial pressure effect cardio-deceleration utilizing pressoreceptor mechanisms located in the carotid sinus and aortic arch areas. It has been shown that a relatively small part of the response is on the basis of decreased venous return during the period of fistula closure. The results of separate experiments conducted on different days are shown in figures 3 A and 3 B. A 7.7 mg. per kg. dose of procaine (500 mg.), given intravenously as a 0.1 per cent solution, failed to block the reflex bradycardia resulting from manual closure of the fistula. The procaine infusion resulted in flushing, blurring of vision, and slurred speech. The last ten minutes of the infusion was given at a rate of 20 mg. per minute. The same procedure was repeated the following day using 4.6 mg. TEAC (300 mg.) in 5 cc. isotonic saline solution. Completed over a five minute period, the intravenous injection of TEAC resulted in flushing, tingling sensations in hands and legs, and the subject complained of a garlic taste. A resting heart rate of 102 per minute increased to 128 per minute; a blood pressure decrease from 144/56 to 128/62 was recorded. Five minutes after completion of the TEAC injection, heart rate and blood pressure were at the preinjection level. In contrast to procaine, a nearly complete blockade of the reflex bradycardia resulting from manual occlusion of the fistula could be demonstrated.

Case 2. E. M. (170–023), a 74 year old man weighing 65 kilograms, and demonstrating a hypersensitive carotid sinus reflex one year following radical neck dissection for lip carcinoma metastatic to regional cervical lymph nodes, showed a profound bradycardia, snoring, and unconsciousness, with a 15 to 30 mm. decrease in systolic blood pressure during periods of vigorous massage over the carotid bulb. The cardiac slowing typically preceded the onset of central nervous symptoms, and the decrease in blood pressure usually outlasted the
Fig. 3. Comparative effects of procaine and TEAC. Pressoreceptor reflex arc activity in unanesthetized man, reflex bradycardia elicited by manual closure of an arteriovenous fistula: (A) intravenous procaine, 500 mg., (B) TEAC, 300 mg. See text for further explanation.

Snoring and unconsciousness resulting from sinus stimulation. The results of two experiments are illustrated in figures 4 A and 4 B. Prior to ganglionic blockade following 5 mg./kg. TEAC, a five second asystole resulted from carotid sinus stimulation. Following the blockade, a fourteen second stimulus produced bradycardia and central nervous system symptoms which were less
marked than the pre-injection responses. Twenty minutes following TEAC blockade, a twenty-three second stimulus was well tolerated, with minimal alterations in heart rate and without loss of consciousness or alteration in blood pressure. A 7.7 mg./kg. dosage of procaine (500 mg.) failed to effect a comparable ganglionic blockade.

Receptor Mechanisms. Carotid-Aortic Chemoreceptor Mechanisms. While the physiologic stimulus for the chemoreceptors is hypoxia, and a clear morphologic similarity between chemoreceptors and ganglion

cells in the autonomic system does not exist, the chemoreceptors can be activated by cholinomimetic compounds such as acetylcholine, or by nicotine. The hyperpneic response to intra-carotid injection of acetylcholine or nicotine in the atropinized animal can be blocked effectively by TEAC (21, 23). The cardiovascular over-shoot and pressor response to direct excitation of ganglion cells at synapses in the autonomic system are blocked by the TEAC administration. Only a
partial blockade of the hyperpneic response was accomplished by a 12 mg./kg. dose of procaine, and there was no discernible influence upon pressor response or cardiovascular over-shoot. The incomplete procaine blockade was of less than twenty minutes duration. A 6 mg./kg. dose of TEAC produced chemoreceptor and ganglionic blockade which was complete for forty-three minutes following the injection.

Carotid-aortic Pressoreceptor Mechanisms. Results of the experiments that have been described under Synaptic Transmission in Autonomic Ganglia indicate that all components of the reflex arc remained functionally intact after the prior administration of large doses of procaine in the acute preparations which were studied, in unanesthetized animals, and in the human subjects.

Pulmonary Stretch Receptors. There was no change in respiratory pattern following procaine administration which would suggest a deafferentation had been accomplished.

Alterations in threshold and the responses of isolated sensory receptor units following the injection of a variety of pharmacologic agents, as well as procaine, have yet to be studied utilizing the different methods of direct excitation of single sensory units described by Bishop (38), Gray and associates (39, 40), or Maruhashi, Mizuguchi and Tasaki (41). A clinical study of procaine effects upon pain threshold in normal and hyperalgesic burned skin was made by Kibler and Schnaper (42) using the Hardy-Wolff-Goodell radiant heat technique. In adult human subjects, these investigators were unable to demonstrate a significantly elevated threshold to radiant heat in either normal or traumatized skin following doses of 1,000 mg. of procaine administered over a fifty-five to seventy-five minute period.

Discussion

The results of the present experiments, examining the peripheral nervous actions of procaine under a variety of conditions and with a diversity of testing procedures, would suggest that the anesthetized animal, the chronic preparation, and intact unanesthetized man alike show no significant alterations of function in peripheral neurones, various effector organs, or transmission at preganglionic autonomic synapses from procaine concentrations achieved with drug dosages approximating the clinical procaine unit of 4 mg. per kilogram of body weight.

This is not to deny the peripheral nervous actions of procaine as a depressant drug (5). With increasingly large dosages, procaine becomes almost ubiquitous in its sites of action. Primarily and first affected is the effector side of the reflex arc, where cholinergic mechanisms are operative. Cardiac vagus block and interference with neuro-effector transmission to skeletal muscle are relatively early changes manifest with increasing dosages of procaine. Such effects occur in 10 mg./kg. dose range and precede discernible influences upon gangli-
onic transmission or peripheral nerve conduction by a wide margin. In fact, to exert even minimal effects upon these more resistant areas in the peripheral nervous system, extremely large dosages of procaine in the order of 25 to 50 mg./kg. or more, are required.

The capacity of intravenous procaine for selective action in the peripheral nervous system is unimpressive when compared to such blocking agents as TEAC, Banthine\textsuperscript{®} or nicotine. The relative ineffectiveness of the procaine unit (4 mg./kg.) in altering peripheral nervous system actions at any point was a most striking negative result when considered in the light of well-documented clinical response to dilute intravenous procaine in the treatment of chronic pain syndromes, of fixed or radiating pattern, of weeks, months, or years' duration, and refractory to all other presently known pain medications and to orthodox neurosurgical ablative procedures.

While these statements can be made with reasonable assurance, in the absence of direct experimental evidence similar inferences are unwarranted regarding the neuropharmacology of free nerve endings, specific receptor-afferent neurone transmission, or central neuronal-synaptic mechanisms. A lack of specific sensory receptor information should be noted. Neither qualitative nor quantitative studies of procaine effects upon isolated sensory receptor unit activity are at hand. The inadequacies of the Hardy-Wolff-Goodell method for quantitating the pain threshold (43) do not discount completely the evidence from clinical studies of normal and burned skin which show no alteration in pain threshold following 1,000 mg. dosages of procaine (42). From the available evidence it would seem unlikely that the function of free nerve endings or cutaneous receptors subserving pain are significantly altered by procaine concentrations achieved with 4 mg./kg. intravenous infusions.

The experimental conditions of acute animal studies under anesthesia have the limitation of artificiality, and the possibility exists that procaine effects might occur in the peripheral nervous system of the normal unanesthetized preparation, or in man with pain, which are masked by the depth and type of anesthesia used in these experiments. For this reason, quantitative application of such data to clinical problems is difficult. Still, the few clinical studies that we have made of reflex arc activity, physiologically activated in intact unanesthetized subjects, as well as the reflex arc studies in chronic animals, support the generalization that was made from the analysis of results in the acute animal experiments—functional adequacy of all peripheral nervous elements concerned in normal reflex arc activity after intravenous administration of the 4 mg./kg. procaine unit.

There will always be room for argument when quantitative application to clinical problems is inferred from studies of anesthetized animals using artificially excited nervous structures. The massive synchronized barrage of nervous impulses which follows electrical stimula-
tion of peripheral nerves, dorsal or ventral roots, or central neurons has rare counterpart in normal physiology and the responses of naturally activated nervous structures. By using light anesthesia, a variety of anesthetic agents, physiologically activated as well as artificially activated reflex responses, and both anesthetized and unanesthetized preparations, the attempt has been made to minimize these objections.

The possibility should also be considered that peripheral nervous actions may have occurred which were not revealed by relatively insensitive recording methods. In particular it would be desirable to have quantitative information regarding a change in total sensory input from all sources following drug infusions.

A recent review of the neuropharmacology of peripheral nerve (5) has emphasized the significance of individual susceptibility of various points in the nervous structure of the central and peripheral nervous systems. This fact becomes significant when the extreme dilution that follows the intravenous administration of 0.1 per cent procaine solution is considered. Tomans observes that the full blocking concentration of procaine is 10 millimols for frog sciatic nerve, the molarity of the 1 per cent solution customarily used for local anesthesia is 40, and plasma levels required for intravenous analgesia are in the order of 0.001 mM. While some information is available regarding inactivation and excretion of procaine, and the metabolic pathways pursued following its administration, something more or less is known about specific rates of distribution or selectively high concentrations in nervous or non-nervous tissues by procaine, DEAE and PABA. Using a diazo-dye tracer technique, Fulton (30) observed the general distribution of procaine-brown within elements of the central nervous system following its intravenous injection. There is, however, no detailed body of information available at this time which relates to the differential concentration of procaine or its enzymatic breakdown products within specific areas of the neuraxis or at special sites in the peripheral nervous system.

Selectively high concentrations of procaine might occur at various points in the peripheral nervous system, in several ways. It could occur as a manifestation of differential permeabilities of various cell membranes. This situation would not require alterations in capillary or cell membrane permeability characteristics, only the normal processes of differential distribution and cell fixation. In general, the distribution of local anesthetics absorbed into circulating blood is the same as that of all other non-volatile anesthetics (44). A proportion is absorbed and fixed by nervous tissue, a part is deviated by its absorption and fixation in non-nervous tissues; a part is eliminated by the kidney, and the remainder is detoxicated by the liver and serum enzymes. If selectively high concentrations of procaine occur at any point in the peripheral nervous system following the intravenous ad-
ministration of dilute solutions, these studies have given no results which can be interpreted as supporting this possibility. A second explanation for abnormally high concentrations of procaine at the periphery would invoke the hypothesis of a changed vascular permeability at a site of injury, inflammation, edema and pain, with locally anesthetic concentrations in the area of injury (6). This peripheral saturation theory might explain the pain control in some instances of acute injury. It would seem that such is almost certainly not the case in those chronic pain states where the genesis of pain cannot be well explained on the basis of abnormal neuronal states at the periphery alone (13, 14), and little or no evidence exists that there is an area of associated increased vascular permeability and local injury.

The question arises whether the procaine effect is exerted through one of its metabolic products, DEAE or PABA. The pharmacologic actions of DEAE are quantitatively different from procaine effects in most respects (45). Papper et al. (46) have demonstrated minimal analgesic effects and local anesthetic properties for both DEAE and PABA, while Graubard and Peterson (9) have stated that DEAE is not so effective as procaine when given in millimol equivalents. Pharmacologically less active than procaine, where procaine and DEAE actions overlap, there would seem to be possible significance to the studies of the physiologic disposition of DEAE made by Rosenberg et al. (47). High concentrations of DEAE and relatively persistent plasma levels were demonstrated following intravenous procaine infusions. Three hours following the injection of 11 Gm. of DEAE, tissue analyses were done which demonstrated extensive localization of this substance in nervous tissue. A brain concentration of 223 mg./kg. was observed, in contrast to plasma concentrations of 70 mg./kg. Peripheral nervous tissue concentrations were not reported in this study. Almost eight hours were required in man for the near-complete metabolic disposition and renal excretion of a single dose of DEAE.

Finally, the possibility of neurotoxicity must be considered with the actual destruction of nervous elements following intravenous procaine administration. Rabinovici (48) has shown that anatomic dissolution of sympathetic ganglia cells may follow the local infiltration of 1 per cent procaine solution in proximity to such nervous tissue. It is conceivable that an indiscriminate mass destruction of nervous tissue might occur following the intravenous infusion of dilute procaine solutions, so as to alter the total input-output ratio of the nervous system and thus modify perception. On the other hand, a highly selective destruction of particular cell groups that are essential to pain perception might be postulated. As a possible explanation for the long-lasting effects of dilute procaine infusion in cases of chronic pain, neurotoxicity would seem an unlikely possibility. There is neither contrary nor supporting evidence for it at this time.
As an alternative to the peripheral saturation theories of procaine action, the clinical response to dilute procaine infusions might be related to a depression of activity within the neuraxis, where complex multineuronal circuits, as well as "classical" sensory pathways, would seem essential to the total pain experience. Such a hypothesis focuses attention upon central pain mechanisms (13, 15). Experimental data and discussions relative to this possibility are subject matter for a second paper which deals with the central nervous actions of procaine.

SUMMARY

A neuropharmacologic study of the peripheral nervous actions of procaine has been made.

In the intact anesthetized animal, the intravenous administration of procaine resulted in little or no measurable change in functional integrity of various elements of the peripheral nervous system when the clinical procaine unit of 4 mg. per kilogram of body weight was approximated.

Pharmacologic dosages of 10 to 50 mg./kg. of procaine exerted minimal to significant blocking actions at various points in the peripheral nervous system of the anesthetized preparation.

The functional integrity of the reflex arc was not measurably altered in the unanesthetized animal or intact man following dosages of procaine of less than 10 mg./kg.

These results call in question the peripheral action theories which have been invoked to explain the clinical response to dilute intravenous procaine infusions for the chronic pain syndromes.

Alternative explanations require not only consideration of central procaine actions upon classical sensory pathways within the nervous system, but also a consideration of drug effects upon a central brain stem and interneuronal cortical system with multisynaptic organization.

REFERENCES


Preliminary Program
1955 Annual Meeting
American Society of Anesthesiologists, Inc.
Statler Hotel, Boston, Massachusetts
October 31 to November 2, 1955
Monday, October 31, 1955

Morning: Panel Symposia:
The Endocrine Factors in Response to Anesthesia and Surgery:
Basic Concepts—Arnold Relman, M.D.
Effects of Anesthesia—Leroy Vandam, M.D.
Stress of Surgery—D. H. Nelson, M.D.

General Scientific Session:
Further Investigations of Electrocarcinosis as General Anesthesia in Animals and Man—Robert C. Knutson, M.D., Fae Y. Tichy, M.D., Werner P. Koells, M.D., and John H. Reitman, M.D.
Studies on the Work of Breathing in Relation to Anesthetic Procedures—Nancy Wu, M.D., William F. Miller, M.D., and Nellie R. Luhn, M.D.
Delineation of Protective Mechanisms in Hemorrhagic Shock—Solomon G. Hershey, M.D., B. W. Zweifach, Ph.D., and W. Antopol, M.D.

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