THE ACTION OF PROCAINE, SALICYLATE AND BENZOATE OF SODIUM ON THE EXCITABILITY OF SKELETAL MUSCLE AND OF NERVE *

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INTRODUCTION

In a previous paper (1) it was shown that the sciatic nerve as well as the muscle of frogs remains excitable for two or three weeks when kept in saline solution near 0 C. It was decided to determine whether the survival time of the nerve could be prolonged by suspending its excitability by procaine, and whether this agent has similar actions on skeletal muscle. The prolonged exposure would also give opportunity for more uniform penetration than is usually secured in acute experiments on excised structures. This would subject all the fibers to more uniform concentrations of procaine, and render dilute solutions more effective. This study brought out features of the action of procaine which appear to have been overlooked and which place these actions in a somewhat novel light. Briefly, these features show that the depression of excitability by procaine is reversible only within rather narrow limits; that procaine depresses the excitability of skeletal muscle to nearly the same degree as that of the motor nerve fibers, given effective penetration, and that the peripheral action of procaine appears to differ only in degree from that of sodium salicylate and benzoate and a variety of other substances. This suggests that nerve depression by local anesthetics is not a fundamentally distinct phenomenon but rather a manifestation of general "protoplasmic" depression, which owes its practical usefulness to a favorable therapeutic index of anesthetic potency as against local irritation and systemic toxicity. The striking features of this specialized use have so overshadowed the unspecialized aspects of the actions that they have been neglected, especially as the conditions of clinical anesthesia purposely aim to concentrate the effects on the sensory fibers and to insure reversibility. Suitable experiments on living animals, however, show that anesthetic concentrations of procaine depress and abolish the response of skeletal muscle to direct stimulation if good contact is secured either by injecting the

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procaine directly into the muscle tissue, or by injecting it into the peripheral end of a ligated artery. This direct muscular action may play a significant role in the depression of proprioceptive tonus and in the relief of spasmodic contractures; although the investigations of G. Liljestrand and B. Magnus (2) showed that circumscribed decerebrate and tetanic rigidity is completely relieved by the injection of procaine in doses which do not interfere with voluntary movements or with response to stimulation of motor nerves. This shows that the afferent proprioceptive fibers have a relatively high susceptibility to procaine. In our experiments with clinical concentrations, however, the depressive action was sufficiently strong to weaken or suppress response of the muscle to direct stimulation.

Experiments on animals and on ourselves confirmed the local anesthetic action of sodium salicylate and benzoate although they would not be good substitutes for procaine, since they are considerably less potent and the salicylate is more irritant.

**Effects on Excised Nerve-Muscle Preparations**

These investigations were made on preparations of the sciatic nerve and gastrocnemius muscle of frogs, immersed in a Ringer salt solution kept near 0°C. The preparations were stimulated with the platinum electrodes of a Harvard induction coil, placed either on the nerve or directly on the muscle, noting the degree of response to stimuli of graded intensity. For observations on the nerve trunk, the sciatic nerve alone was immersed, leaving the muscle outside the solution in a simple moist chamber. The observations on solutions containing drugs were checked against the contralateral preparations in saline solution to which a drug was not added.*

Survival of the nerve and muscle was not prolonged by brief or continued sojourn in any concentration of procaine hydrochloride. All concentrations that have any effect at all produce progressive depression of response to stimulation and shorten the survival time. The response of muscle to direct stimulation is almost quantitatively parallel to the depression of response to nerve stimulation. The speed and degree of the depression increase with the concentration: Full excitability of the nerve muscle, with the secondary coil at 12 cm., is preserved in 1:250 concentration for twenty to forty-five minutes; in 1:500 for seventy-five to one hundred minutes; in 1:1000 to 1:2500 for three and a fourth hours to one day. With a concentration of 1:5000 to 1:10,000, the excitability is the same as when saline solution is employed. Inexcitability with the coil at 0 cm., is reached within one day with 1:250 to 1:2500. With a solution of 1:5000, the procaine preparation

* This portion of the research formed part of investigations on the effects of chemical substances on survival tissue, which contain more details (Sollman, T.: J. PharmacoL & Exper. Therap. 89: 14-25, 1947).
remained excitable for twelve to fifteen days, the same as the control preparation in unpoisoned Ringer solution.  

**Reversibility by transfer to unpoisoned Ringer solution** seems to depend on the concentration and the time of contact more than on the degree of depression. With a proportion of 1:250, good recovery occurred after one hour; with 1:500 after 150 minutes, not after a day of immersion. Only partial recovery occurred after one day in a 1:1000 solution, and no recovery after four days.

*Sodium salicylate and benzoate* appear to act on nerve and muscle qualitatively like procaine, as do also the phenols and quinone. Balancing the degree and speed of action with various concentrations, and using procaine hydrochloride as the unit, the relative potency averages as follows: sodium salicylate 1; sodium benzoate 0.8; phenol 0.5. Paraaminobenzoate, 1:100, and sulfanilamide, 1:1000, were not depressant.

Kubota and Macht (3) in 1919 had shown that the excitability of the gastrocnemius muscle of the frog and rat to direct stimulation decreases in solution of cocaine, procaine and some other local anesthetic agents. The contractility is depressed also and the onset of fatigue is hastened. With the frog muscle, immersion in 1 per cent procaine hydrochloride abolishes excitability in fifty to 130 minutes.

**Depression of Skeletal Muscle by Intra-arterial Injection**

As a comparative test of direct muscular depression by procaine hydrochloride, sodium salicylate and sodium benzoate, the solutions were injected into the peripheral end of the ligated femoral artery of rabbits, testing the response to faradic stimulation applied to the saphenous nerve and to the exposed muscles. The operative field was anesthetized by infiltrating Scarpa’s triangle with the same drug.

In typical experiments, intra-arterial injection of *procaine hydrochloride*, 5 cc. of 2 per cent solution, raised the threshold for reflex response from more than 12 cm. to less than 4 cm.; for direct muscular response from more than 12 cm. to 4 cm., distance of the secondary coil. With intra-arterial injection of 2 cc. of a 5 per cent solution of *sodium salicylate* the threshold for reflex response was raised from 10 cm. to 6 cm.; for direct muscular response, from 12 cm. to less than 6 cm. With intra-arterial injection of 2 cc. of a 5 per cent solution of sodium benzoate the threshold for both reflex and direct response was raised from 12 cm. to 8 cm.

It is seen that the three agents depress the direct muscular response equally as well as the reflex response. The potency of procaine hydrochloride is materially greater than that of sodium salicylate and sodium benzoate.
DIRECT DEPRESSION OF MUSCULAR Tonus IN "PSEUDEHRE'NIA"

The clinical use of local anesthetic agents in cases of spasms of skeletal muscles involves in the first place the selective depression of the highly susceptible afferent proprioceptive fibers. F. Bremer and Titeca, in 1930 (4) confirmed the work of Liljestrand and Magnus, in 1919 (2), that these may be paralyzed by injection of procaine without interfering with reflex movements. Larger doses may be used clinically, however, and it is conceivable that the action may then involve the muscle directly. This was investigated on the "pseudohernia" experiment, the bulge which appears in the abdominal wall of guinea pigs by relaxation of muscular tonus when a local anesthetic solution is injected subcutaneously in this region (5).

In the guinea pig, a bulge was produced by injection of a total of 3 cc. of 1 per cent procaine hydrochloride solution. In the course of fifty minutes the rectus muscle was exposed by a small incision and stimulated directly. It responded at 8 cm. but not at 10 cm., while muscle normally responds to 12 cm. After two and a half hours 12 cm. produced a sensory response but no local muscular twitch. It appears, therefore, that this dosage of procaine depresses the muscle response directly, and that this depression outlasts the muscular paralysis. Similar results were obtained in the rabbit by 1 cc. of 0.2 per cent procaine hydrochloride, stimulating through the intact skin with stronger currents, and in the guinea pig with 1 cc. of a 2 per cent solution of sodium salicylate. Sodium benzoate, 1 cc. of a 5 per cent solution did not produce a definite bulge or raise the threshold for either direct or reflex response. It appears that the "pseudohernia" of procaine involves depression of muscle as well as nerve; indeed the direct effect on muscle is greater than on nerve. Loewe's original demonstration, made with smaller doses, presumably involved chiefly the afferent fibers.

Similar effects are produced by administration of salicylate of sodium, 2 per cent, but were not demonstrable by sodium benzoate, 5 per cent.

PRACTICAL EFFECTIVENESS OF SALICYLATE AND BENZOATE OF SODIUM FOR LOCAL ANESTHESIA

Operative infiltration anesthesia was observed during operations for the exposure of the femoral artery and of the sciatic nerve of rabbits. Satisfactory local anesthesia was obtained with a 0.2 per cent solution of procaine hydrochloride, and with 2 per cent and 5 per cent sodium salicylate, but only light anesthesia resulted when a 5 per cent solution of sodium benzoate was employed.

Canthus infiltration was proposed by Tatum in 1931 (6), as a criterion for subcutaneous anesthesia. Injection of 1 cc. of a 5 per cent solution of sodium salicylate into the outer canthus was found to
abolish the winking reflex; neither a 2 per cent solution of salicylate nor a 5 per cent solution of sodium benzoate suppressed the reflex.

Endermic injection in human beings was tested by injecting the solution into the epidermis of the flexor surface of the forearm so as to produce wheals each 5 to 8 mm. in diameter; three tests each were made with saline solution in the controls, sodium benzoate, 2 per cent solution, and sodium salicylate, 2 per cent solution. Sensory irritation, manifested by brief smarting, was produced by the benzoate and somewhat more by the salicylate, but it was not serious. There was no visible inflammatory reaction.

Sensation was tested in various ways; the best results were obtained by light touch with the point of a pencil. This revealed slight but definite decrease of sensation in the wheal made with the salicylate solution, and doubtful decrease in that made with the benzoate solution.

Conjunctival anesthesia was tested by dropping the solution into the lower conjunctival sac of rabbit. A 5 per cent solution of salicylate did not appear to diminish the response to touch.

Integrating these lines of observations, it appears that sodium salicylate in 2 per cent solution could be used for injection anesthesia, but that it is materially inferior to procaine, being less potent and more irritant. The anesthetic action of sodium benzoate is demonstrable but too feeble for practical use.

ATTEMPTS TO DEMONSTRATE IRREVERSIBILITY OF PROCAINE IN LIVING ANIMALS

The experiments with excised nerve and muscle show that the paralysis resulting from procaine hydrochloride becomes irreversible if the relatively high concentrations act for relatively long periods. These limits would not be attained in routine clinical applications, in which the time of contact is limited by the removal of the procaine through the circulation.

Prolonged Application to the Exposed Sciatic Nerve.—To obtain some idea of the margin of clinical safety, the time of contact was intentionally prolonged by instilling a 2 per cent solution of procaine hydrochloride at frequent intervals into the sulcus in which the exposed sciatic nerve lay in a bed of cotton soaked in the solution. This procedure lowered materially the threshold of response to electric stimulation, but reflexes were strong at 6 cm. Application of the solution was continued for three and a half hours, with the threshold kept at about 10 cm. The animal was then released; its leg dragged for four and a half hours, but was normal by the sixth hour. The conditions were evidently not sufficiently drastic to produce irreversible depression.

Procaine with Prolonged Epinephrine Ischemia.—If 1 cc. of 1:1000 solution of epinephrine is injected around the vessels at the root of the
ear of rabbits, the circulation of the ear is impeded for hours. This procedure would greatly delay the absorption of procaine hydrochloride from the ear, and it was conceivable that the procaine would remain long enough to render its depression irreversible. The opposite ear was injected with epinephrine without procaine. This control experiment shows that the sensitivity of the ear to faradic stimulation is not diminished by ischemia of at least twelve hours' duration, induced by the injection of epinephrine, 1 cc. of 1:1000 solution, repeated in six hours.

The injection of 1 cc. of 5 per cent solution of procaine hydrochloride after the injection of epinephrine abolished the response to strong faradic stimulation with the secondary coil at 0 cm. for the six hours during which the animal was observed. Epinephrine was again injected in both ears, and procaine in the ear in which it had been injected previously. When next observed, twenty-four hours after the first injection and sixteen hours after the second injection, both ears were fully sensitive. This experiment, therefore, had failed to make the procaine action irreversible, confirming a wide margin of practical safety in this respect.

**Summary**

Procaine hydrochloride depresses and abolishes the excitability of skeletal muscle as well as that of motor nerve fibers of the frog. The depression of both tissues are closely parallel if the action is slowed by diluting the solutions so as to insure effective concentration.

Procaine depression of excised muscle and nerve is reversible by washing only within rather narrow limits, depending on the concentration and time of action more than on the degree of depression.

The depression of excitability grades so smoothly into death that it appears attributable to general protoplasmic toxicity rather than some fundamentally distinct "narcotic action."

Apparently, identical depression of nerve and of muscle is produced by sodium salicylate and benzoate, by phenol, by hydroquinone and by many other agents. The potency of sodium salicylate in excised preparations is of the same order as that of procaine; sodium benzoate and phenol are somewhat less potent; para-aminobenzoate and sulfanilamide are not depressant in equivalent concentrations.

Direct depression of skeletal muscle is also observable in living animals if procaine hydrochloride in 1 or 2 per cent solution is injected intramuscularly or intra-arterially. It may even be somewhat more potent than the depression of pain sensation, and plays a conspicuous part in the depression of proprioceptive tonus in the "pseudohernia" experiment.

Satisfactory operative local anesthesia can be produced by injection of 2 per cent sodium salicylate, but it is materially inferior to procaine
since it is less potent and more irritant. Sodium benzoate produces too light anesthesia for practical use.

Conditions in the living body prevent the local paralysis by procaine from becoming irreversible, even when its removal by the circulation is made good by continued application or greatly diminished by blocking the vessels with epinephrine for long periods.

REFERENCES


(Continued from page 187)

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4. The Therapeutic Uses of Intravenous Procaine. Milton C. Peterson, M.D., Anesthesiologist, Research Hospital, Kansas City, Missouri.

11:30 a.m.—12:00 Noon. General Discussion.
12:00 p.m.—1:30 p.m. Luncheon—Hotel President. Round Table Discussion.
1:30 p.m.—1:45 p.m. Business Meeting—American Society of Anesthesiology, Junior Ballroom, Hotel President.
1:45 p.m.—3:30 p.m. Junior Ballroom, Hotel President. C. R. McCubbins, M.D., Presiding.
1:45 p.m.—3:30 p.m. Symposium of Spinal, Regional and Therapeutic Nerve Block.
1. Sympathetic Block and Its Practical Application for Therapeutic Uses. Technic and Principles. R. M. S. Barrett, M.D., Chief of Anesthesia, St. Louis University, St. Louis, Missouri.
2. The Utilization of Regional Anesthetic for Therapeutic Procedures. Technic and Principles. Charles F. McCuskey, M.D., President, A.S.A., Chief of Anesthesia, University of Southern California, Los Angeles, California.

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