EXPERIENCES WITH PROCAINE HYDROCHLORIDE*

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ONE HESITATES before adding yet another contribution to the extensive literature on this subject. However, as procaine is still the most widely used local anaesthetic, and as its mode of action when given intravenously is still debatable, the present communication may not be amiss, particularly as the cases here presented may help to clarify its pharmacological action in man. The ultimate tribunal for any drug, of course, must be its effects on man, *particularly diseased man*.

Intravenous procaine has been used at one time or another for a large number of medical and surgical conditions, either as the sole treatment or in conjunction with other methods, or for its analgesic properties alone. Such protean possibilities indicate that it must at least affect the nervous and/or the cardiovascular system, and also that the diseases that respond in some degree or other must, not surprisingly, be involved for at least part of their patho-physiology with one or both of these systems.

Pharmacologists are agreed that procaine relaxes arteriolar spasm (1). It is also established that procaine has a weak relaxing effect on striated muscle by diminishing the production of acetylcholine at the neuromuscular junction. In a similar manner it also depresses ganglionic transmission. It is stated (2) that the concentration of procaine in injured tissue following intravenous administration may be six to eight times that of normal tissue. Some authorities believe that this concentration is sufficient to produce analgesia and sympathetic blockade in certain cases, by acting on pain and sympathetic fibres especially at or near their fine unmyelinated endings. Procaine is also a myocardial depressant and has a quinidine-like action on the heart. The blood pressure may be lowered by the action on the myocardium and arteriolar dilatation. Procaine when taken orally, also relaxes smooth muscle, for example, cardiospasm, gastrospasm and pylorospasm, possibly by a direct anaesthetic action on sensory receptors, thus abolishing local motor and tone reflexes.

Procaine is destroyed chiefly by the liver, but also in the blood by procaine esterase. Procaine esterase, probably identical with serum cholinesterase, is inhibited by prostigmine. Procaine may also counteract the prostigmine effect on curarised muscle (3). In the normal person a "procaine unit," 4 mgm. per kg., is completely destroyed in 20 minutes.

Procaine was usually administered in doses of 250 to 1,000 mgm. in a 0.1 per cent or 0.2 per cent solution and as fast as the patient could tolerate it without undue side effects. These side effects consisted of anxiety, nausea, vertigo, tachycardia and tachypnoea. Subjective warming, flushing and perspiration were considered to be normal effects. At first, the patient's blood pressures were

*Presented to the British Columbia Division of the Canadian Anaesthetists' Society January 20, 1956

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taken regularly and oxygen was administered if the patient had tachypnoea. It was noted, however, that such attention increased the patient's anxiety at times, so much so that two young patients developed hyperventilation tetany. This was mistaken at first for a procaine reaction. Latterly a more casual attitude was taken towards the treatments.

PROCAINE IN ASSOCIATION WITH GENERAL ANAESTHESIA

Some seven years ago many patients were given procaine during their anaesthetics (pentothal, curare, N_2O), usually near the end in an attempt to relieve postoperative pain. Evaluation in this respect was difficult, but certain effects appeared to be unequivocal. In larger doses (up to 2 grams) there was a general potentiation of the effects of the anaesthetics. Patients slept longer after operation and some were depressed to the point of cyanosis. These patients should have received less pentothal and curare, both of which are potentiated by procaine. It was soon found also that some hypertensive patients under anaesthesia would have a precipitate but apparently harmless fall of blood pressure (e.g., from 200 to 100 mm Hg systolic) shortly after starting intravenous procaine. This is not recommended, and procaine must be carefully administered to hypertensive patients under anaesthesia. More recently, it was also found that 150–200 mgm. of procaine given in 3 to 4 minutes obviated the need for further curare to sew up the peritoneum following laparotomies. Excellent relaxation could be obtained in this manner. In moderate dosage (up to 1 gram) it was noted that thyroidectomy patients did particularly well, having much less pain and restlessness than usual. Nearly every one of these patients anaesthetized by me has received procaine since this observation was made. One case in particular merits attention.

A very toxic, seriously ill, middle-aged woman, with auricular fibrillation, received procaine during the operation. She did fairly well the same day, but the next morning she was extremely agitated, perspiring profusely, with eyes bulging. She was given procaine again with remarkable improvement apparent by the end of the treatment.

Although no particular point was made about the procaine at any time, and the nurses were usually unaware of its administration, it was not uncommon for them and others to say they never saw a thyroid case do so well. The P.A.R.R. nurse, with four years' experience, states emphatically that the procaine patients were much quieter than the others. They were quietly awake with little or no discomfort and did not need a sedative for four hours or more, and then usually for a sore throat (i.e., inside).

It was also unequivocal that many patients undergoing plastic surgery did better when given procaine.

One 2½-year-old boy had to have multiple plastic procedures performed on his hand. He was given intravenous procaine with each anaesthetic with seeming benefit. By the next morning, this normally happy boy would be glum and refuse to eat his breakfast. At this time he would be given 400–500 mgm. of procaine in 150 cc. of water by rectal drip. Within 10–15 minutes of starting the drip he would be happy again and calling for food.

The original purpose of the procaine in this case was to assist healing. Other small children undergoing burn dressings or debridement were handled with rectal procaine also. Patients who had undergone hysterectomy had much less pain than expected when procaine was administered intravenously near the end of the operation. On the other hand, it was thought that patients with spinal operations received little or no relief postoperatively from a single intravenous dose of procaine.

For reasons indicated in the introduction, prostigmine is said to be contraindicated when procaine is or has been used. Some years ago, before being aware of this presumed contraindication, I gave prostigmine in 0.5 to 1 mgm doses to several patients who had just received or were receiving procaine. There was no demonstrable ill effect.

INTRAVENOUS REGIONAL PROCAINE ANAESTHESIA

Some 25 cases of injury of the upper extremities were handled by the intravenous regional method of Bier (modified). Into the vein of the arm, which had been drained of blood, 20-40 cc. of 1 per cent procaine were injected. A tourniquet confined the procaine to the area. This gave very effective anaesthesia as long as the tourniquet was on. On removal of the tourniquet—after half an hour or more—the only sign of toxicity noted was an occasional tachycardia. Sensation returned in 3-7 minutes. With one patient, who had had 20 cc of 1 per cent procaine injected, the tourniquet slipped at about three minutes, the patient vomited and had a tachycardia, but showed no other ill effects. The main purpose in mentioning these cases is to indicate that detoxification does occur either in the tissue or in plasma or both.

After operation

Some patients with respiratory morbidity were helped in keeping their chests clear. Although the patients sometimes denied any relief, it was noticed that they could cough up secretions more readily. The pain and oedema of post-operative hand injuries were dramatically improved on occasion, as much as $\frac{3}{4}$ inch of oedema of the back of the hand, which was pressing on the cast, being removed in an hour.

Eclampsia

One very severe post-partum eclamptic was given two intravenous procaine treatments in twelve hours. She went blind during the second infusion and was immediately given a caudal block with benefit. This was repeated twice; there was improvement after each block, with complete recovery in about a week. It is thought that the intracranial pressure was so high that vaso-dilatation from the intravenous procaine increased it beyond the critical point. Less severe cases might well benefit as has been reported.

Burns (4)

Since 1944 all recent burns have had their debridement and dressings done under procaine analgesia. There is certainly no doubt whatever of the efficacy in these cases. Patients become comfortable and co-operative as long as normal skin is avoided and a reasonable gentleness used. The rate of drip has to be

adjusted almost from minute to minute for the best results in these cases. Speeding the drip is effective in as little as one minute. One patient with burns of the face, oedema of the eyelids, and severe blepharospasm opened his eyes spontaneously and almost fully within 90 seconds of the start of the drip.

Fractured Spine and Ribs

Repeated procaine infusions daily or even twelve hourly undoubtedly are of benefit in the therapy of fractured spines and/or fractured ribs. For example.

An old lady with a recent crush fracture of the sixth dorsal vertebra and considerable back and abdominal pain was greatly relieved with each intravenous injection of procaine, and could be ambulant in a few days and discharged from hospital within two weeks. She also received mecostrin* 1½ mgm. intramuscularly t.i.d.

Hypertension

A widow, aged 49, with persistent hypertension, quadrilateral Raynaud's phenomena, headaches, insomnia and nervousness, was incapacitated and had been considered for a sympathectomy which was not done on account of her age. Other treatments had been of no avail and her blood pressure remained at 180/120 despite bed rest and sedation. She was referred for a lumbar sympathetic block to try to improve the circulation in her legs. This was done on one side with 25 cc. of 2 per cent procaine. Her blood pressure came down to 150/90 (it was being checked twice daily), she felt generally much better and all her extremities warmed up. One more procaine intravenous was given, her pressure remained around 140/90 and she looked and felt much better. Her appetite improved and she was discharged from hospital. Her syndrome recurred suddenly two weeks later and she responded similarly to another procaine infusion. She has been generally better since then although her blood pressure is up again.

Another woman aged 35 had a sympathectomy on one side for hypertension. She had an empyema following this and the other side had not been done. Her pressure remained at about 182/108 with considerable elevation above this level at times. She was extremely tense and slept only about four hours a day. She also suffered from severe pounding headaches and recurrent precordial pain. After two intravenous infusions of procaine her average blood pressure was 180/99. This change is probably not significant, but she felt much improved and when seen two years later she said that she had been "slowed down" considerably since the treatments and was decidedly better.

Scleroderma (5)

One woman of 45 with severe progressive scleroderma (hands and forearms especially affected) received temporary benefit with repeated intravenous procaine.

Asthma

One patient with status asthmaticus had subjective relief of dyspnoea for a few hours with 15 cc. of 1 per cent procaine given slowly intravenously.

Brachial Plexus Avulsion

A man of 24 with a recent avulsion of the brachial plexus was in agony and hysterical, his blood pressure was over 200 systolic due to pain and anxiety. Morphine, gr. ¼ repeated, had no apparent effect. He was given one gram of procaine 0.1 per cent intravenously. When about 200 mgm. had run in he became relaxed and co-operative and asked for a cigarette. A few minutes later his respirations had dropped to 4 per

*Di-methyl ether of d-tubocurarine chloride.

minute. The pain returned in about an hour, but was now *controllable* with 75 mgm. of demerol. Another gram of procaine intravenously four hours later also controlled his pain similarly. An extremely difficult situation thus became manageable.

Diuresis and Oedema

One elderly obese hypertensive woman voided large quantities and lost 20 lbs. in weight in a week on intravenous procaine treatment for a pain syndrome. Another patient had marked oedema of the legs which cleared up in the hour during which she received 750 mgm. of procaine.

Fat Embolism

A man of 42 became semi-comatose and incontinent about 40 hours following a fracture of his left mid femur. The next day he developed extensive petechiae and was much the same. A procaine drip (800 mgm.) was administered 48 hours after the onset of the cerebral symptoms. He was less responsive immediately following this but within a few hours he could recognize his wife and answer questions. After a further procaine drip (1 gram) the next day, he improved further and could identify himself. The day following a third procaine drip he was taking nourishment by mouth and continued to improve steadily. There were no neurological sequelae.

This patient responded more rapidly and completely than three other cases of cerebral fat embolism in my practice, which were treated expectantly.

Deafness

A woman of 40 who had been partially deaf all her life (familial) could hear sounds and tones that she had never heard before, during her eighth treatment. This improvement was maintained during her hospital stay at least. She was being treated for a sympathetic dystrophy and the improvement in hearing was completely gratuitous and a surprise to all.

Nerve Pain

The use of procaine in treating segmental neuralgia involving the abdomen has been dealt with elsewhere (6) but some of the following illustrative cases of nerve root pain are included.

A woman of 35 had had severe occipital neuralgia for four months following an attack of influenza. She had been hospitalized and almost completely incapacitated for most of this time. Neck traction and other measures had given no relief. She obtained complete and permanent relief after nine daily intravenous procaine treatments. Interestingly, she often noticed a warm feeling in the sub-occipital area during the treatments.

Another patient had had severe constant pain in her left arm for one year following herpes zoster of the left chest wall. There was a distinct localized scoliosis, concave to the affected side over the nerve roots involved. She had complete sustained relief after three intravenous doses of procaine and the scoliosis disappeared.

Repeated single dose (self-administration following a recent injury) indicates that three grams of procaine per rectum and five grams by mouth are equivalent to one gram given intravenously over a period of 40 minutes. This dose relationship in the case of the rectal route is supported by experience with other cases.

INTERPRETATION

Experience with the above and other situations has convinced the writer that intravenous procaine is a useful adjunct to treatment of many types of cases.

This is by virtue of its capacity to relax spastic arterioles; to deposit relatively high concentrations in oedematous areas, which are due to increased capillary permeability; and to relax skeletal muscle. The relaxation of spastic arterioles allows the arteriolar "pumping action" to function and improves the oxygenation of the capillaries, thus reducing their permeability. Both these effects decrease oedema. In confined areas such as the cranium and the intervertebral canals aggravation may occur due to increased pressure following vaso-dilatation. The deposits of procaine in oedematous areas are sufficient to produce analgesia in some cases by action on the fine terminal pain fibres. These actions all combine to produce relief in musculo-skeletal derangement such as fractured spines. The dramatic effect in recent burn cases is explicable on the basis of the exudation of the procaine in a relatively high concentration. The effect in segmental neuralgia is thought to be due to the lessening and eventual abolition of the oedema of the posterior root ganglia where they lie in the rigid intervertebral foramina, as well as to the analgesic effect and the lessening of the muscle spasm.

Permanent relief, when it occurs, is due to the breaking up of the vicious circles involved, such as pain → muscle spasm → more pain. The vicious circle of sympathetic nerve stimulation → arteriolar spasm → capillary hypoxia → increased capillary permeability → oedema → further sympathetic nerve irritation may also be abolished with persistence. Another common vicious circle in pain cases involves the cerebrum, thus pain → anxiety → muscle spasm → more pain. Control of the pain helps to abolish this element, but the conditioned reflexes developed with prolonged pain may be controlled or broken up with the use of largactil. Muscle spasm, an important part of the first vicious circle, may also be diminished by giving mecostrin, 1½ to 3 mgm., tid intramuscularly. Paravertebral blocks are very useful and often essential in the treatment of nerve root pain.

The improved hearing may be due to the relaxation of the small muscles of the middle ear. Scleroderma has a large vasospastic element, of course.

CONCLUSIONS

Many of the conditions for which intravenous procaine has been used may be handled by other methods. For example, peripheral vascular diseases can be and are handled, equally well at least, with other vasodilator drugs such as priscot or largactil, as well as with anti-coagulants. Post-traumatic vasospasm is also well controlled with vasodilators. Experience so far, however, indicates that largactil alone is not enough for most pain syndromes. Also of course, there are easier ways of producing muscle relaxation for surgery than with intravenous procaine, and brachial block is simpler to perform and more satisfactory than the regional intravenous method of Bier, when dealing with injured hands.

It would seem that intravenous procaine is of value in some pain syndromes, burn cases, fractured spine and ribs, and immediately following thyroidectomy and hysterectomy. It is possibly of value in fat embolism. Others recommended its use in cases of CO poisoning, arthritis and poliomyelitis, for example, and it seems logical that it would help these patients. My own experience is insufficient at present to give an opinion. Intravenous Pontocaine and Xylocaine have been tried but seem inferior in most cases. They gave only temporary relief, possibly

because when given intravenously there is no apparent vaso-dilatation. It is probably the vaso-dilatation that produces the "side effects" with procaine, as well as some of the benefits that accrue.

Finally, my experience and the types of cases which are helped has convinced me that, although procaine has some central effect, the greater part of its action is peripheral. This is borne out by the following evidence. A healthy individual gets little or no analgesia from procaine in therapeutic doses and there is no drop in blood pressure. Intravenous procaine produces unequivocal analgesia of burned areas, whereas immediately adjoining normal skin is as sensitive as usual. The relief in thyroidectomy and hysterectomy cases is explicable on the basis of a very good blood supply and fairly large raw areas, equivalent to a burn. Fresh fractures and segmental neuralgias are relieved on the basis of exudation of procaine into oedematous areas, as well as the relief of vasospasm. The benefit in eclampsia, fat embolism, and hypertension is due to the relaxation of the spastic arterioles and the resultant decrease of oedema.

RÉSUMÉ

On a employé autrefois dans un grand nombre de cas médicaux ou chirurgicaux la procaine par voie endoveineuse, on l'employait seule comme traitement ou, encore, associé à d'autres méthodes ou, exclusivement, pour ses propriétés analgésiques. De semblables possibilités laissent croire que la procaine doit avoir une action soit sur le système nerveux soit sur le système cardiovasculaire et que les maladies qui sont plus ou moins influencées par elle doivent, au moins pour une fraction de leur pathologie, affecter l'un ou l'autre de ces systèmes ou les deux ensemble.

Les pharmacologistes sont unanimes pour dire que la procaine relâche le spasme artériolaire (1). On a également établi que la procaine produit un léger effet inhibiteur sur le tonus du muscle strié en diminuant la production d'acétylcholine à la jonction neuromusculaire et, par le même procédé, elle ralentit la transmission ganglionique. On a établi (2) que la concentration de procaine dans les tissus lésés était de 6 à 8 fois plus élevée que dans les tissus normaux au cours de l'administration par voie endoveineuse. On croit que, dans certains cas, cela est suffisant pour produire une analgésie et réaliser un certain blocage sympathique. Sur le cœur, la procaine aurait, dit-on, une action semblable à celle de la quindine. La procaine pourrait aussi neutraliser l'effet de la prostigmine sur le muscle curarisé.

L'auteur a fait usage de la procaine par voie endoveineuse dans les cas suivants: thyroidectomie, pour produire de l'analgésie et réduire l'œdème des extrémités à la suite de traumatisme ou d'opération, dans l'éclampsie, pour le débridement et les pansements chez les brûlés, pour diminuer la douleur dans les fractures de côtes ou de la colonne, pour produire l'anesthésie régionale (méthode de Bier) dans le traitement de la sclérodermie, de l'asthme, de l'œdème (pour produire une diurèse), dans l'embolie graisseuse, la surdité et les névralgies segmentaires. On croit que le soulagement, dans cette grande variété de pathologies, serait le résultat du pouvoir de la procaine de dilater les artérioles, de se déposer en assez grandes concentrations dans les régions œdématisées et de diminuer la spasme musculaire.

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