PROLONGED LOCAL ANALGESIA WITH BENZOCAINE-URETHANE SOLUTION

BY

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During the last few years much interest has been centred on attempts to find a local analgesic drug or combination of drugs with an action prolonged over several days or weeks (McCleery *et al.*, 1948; Lewis and Thompson, 1953; Davidson, 1953). Such a preparation, if it were proved to be safe and free from undesirable side-effects, would have a wide field of usefulness. Most of the preparations so far advocated, however, including the recently introduced "efocaine" (Puderbach and Shaftel, 1952; Roualle, 1952; Oldham, 1953), have drawbacks and disadvantages which prevent their gaining widespread acceptance.

This paper briefly presents our experiences with a benzocaine-urethane solution, which in our hands has proved eminently satisfactory and free from undesirable side-effects. This solution was first described by Rappaport (1946) and by Spira (1946): its use in this country was referred to by Kohn and Vitali (1950) and by Rutter (1952).

Mechanism of Prolonged Action

The solution used is a simple, easily prepared one. It consists of a solution of benzocaine 2% and urethane 40% in distilled water. In these proportions the solution, though saturated, is stable: dilution with water or by contact with tissue fluids results in the precipitation of the benzocaine in micro-crystalline form. A "depot" is thus formed from which the active agent is slowly absorbed, resulting in a prolonged but strictly localized analgesic action. We have carried out experiments, both *in vitro* and *in vivo*, to confirm that this deposition in crystals does actually occur. Even a small amount of water added to the solution in a test-tube causes an immediate turbidity: by filtration of the precipitate and measurement of its melting-point, we were able to establish that it is indeed pure unchanged benzocaine. In the tissues the crystals may readily be demonstrated by direct examination of thick sections without embedding; their gradual fragmentation and disappearance may be followed by taking specimens (using legs destined for amputation) at increasing intervals of time.

Preparation and Properties

The solution is prepared as follows. To a 40% solution of urethane in distilled water, benzocaine (*para*-aminoethyl benzoate) is added in the proportion of 2%. The mixture is slowly warmed until the benzocaine is dissolved, and is allowed to stand for twenty-four hours. It is then filtered into screw-topped bottles of 20-ml. capacity and sterilized by autoclaving. We have shown that autoclaving does not result in a loss of more than 8-10% of the benzocaine, and that the *p*-amino-benzoic acid produced is quite non-toxic. Once sterilized the solution requires no preservatives and has active bacteriostatic properties against heavy inocula of all the common pathogenic organisms. The solution so prepared is a clear colourless one, with pH of 7.4 and a viscosity of only 1.93 (water equals 1). The low alkalinity

and low viscosity are two of the most valuable properties of the solution in comparison with other preparations recently introduced.

Technique of Injection

The solution being a hypertonic and highly saturated one, and the method of action being that of the laying down of depots of a relatively insoluble active agent, certain precautions are essential in its use. From our own experience and that of others we have evolved the following rules, observance of which is essential if efficient action is to be achieved and undesirable side-effects are to be avoided.

(1) Syringes and needles must all be dry. Even a small amount of water is enough to cause some precipitation of the benzocaine; blocked needles and inaccurate dosage will arise if this precaution is not observed.

(2) Injections into the dermis must be carefully avoided, and superficial subcutaneous injections should be made only into normal healthy tissue. Injection into inflamed areas or into avascular scar tissue may cause necrosis. We have had one case, in our early experience, in which injection into a painful adherent scar resulted in an indolent ulcer which took several weeks to heal.

(3) The injection is essentially a "depot" one, and too large an injection into any one site may lead to the formation of painful nodules and to undue tissue reaction. This applies especially to injections near the skin surface. For most purposes a depot of 1 ml. is the largest which should be made at any one spot. The solution may well be used for the anaesthetization of wound edges by local injection: but instead of the ordinary continuous infiltration technique it must be placed in discontinuous depots of 0.5 to 1 ml., spaced at intervals of about 2 cm. Continuous analgesia will be secured by the overlapping of the small zones produced around each little depot.

(4) Nerve block is in general preferable to local injection, and it is in this field that the solution has its greatest usefulness. Direct injection into the nerve itself is to be avoided, and the aim should be to surround the nerve with a zone of small depots. While up to 2 ml. may be safely injected into the deeper tissues around the nerve trunks, it should be noted that, provided the depots are accurately placed, there is nothing to be gained by larger injections. Absorption is so slow and localized that increasing the size of the depot does not materially increase the area affected, and for almost all purposes individual injections of 1 ml. or less will give the best results. Two closely placed depots of 0.5 ml. each are probably preferable to a single one of 1 ml.

(5) The solution causes a temporary painful reaction, probably due to its hypertonicity. Injection should be done either under general anaesthesia or after preliminary injection of aqueous procaine.

Post-operative Pain Relief

The use of benzocaine-urethane solution for the relief of post-operative pain was first described by Winkler (1951). After experimenting with a number of different techniques we have now adopted a routine block of intercostal nerves 6 to 11, in the mid-axillary line, as the most effective method of achieving relief from the pain of upper abdominal operations. More posteriorly placed injections, which have been used by some workers, carry the risk of tracking of the solution through the intervertebral foramina into the spinal theca; more anteriorly placed ones will miss the lateral cutaneous branches and so fail to produce complete analgesia. A single injection of 1 ml. (or, better, two of 0.5 ml. each, 1 cm. or so apart, made through the same skin puncture) is introduced at the lower border of each rib. Provided care is taken with the accurate placement of the solution, such a regional (bilateral) block produces analgesia over the whole upper abdomen which has always persisted up to the time of removal of the stitches. No effect on the motor function of the nerves has been observed in over 60 cases treated. In those few patients who

have complained of pain in the wound, a careful examination has always revealed that one or more nerves has been missed owing to faulty technique.

We have treated 60 patients by this method after subtotal gastrectomy, and have been greatly impressed by their freedom from discomfort in the immediate post-operative days. To gain some objective measure of the efficiency of the pain relief achieved, we compared the number of injections of sedative (nearly always "omnopon") required by 20 consecutive patients, with that required by a consecutive 20 not injected with the benzocaine-urethane solution. The figures are given in Table I.

TABLE I.—*Number of Injections of Omnopon Required by 20 Non-injected and 20 Injected Patients in First Three Days After Gastrectomy*

	1st day and night	2nd day and night	3rd day and night	Total
Control series	41	35	14	90
Injected series	26	30	16	72

The most striking feature of the comparison is the reduction in the call for pain relief in the first day and night. It is even better demonstrated by an analysis of the individual patients, which shows that whereas none of the 20 non-injected patients got through the day of operation and the succeeding night without having at least two injections for relief of pain, only 4 of the 20 treated patients needed more than one. It is in the first twenty-four hours after operation that the likelihood of pulmonary collapse is greatest, and any reduction in the administration of morphine and similar drugs in this period must be to the patient's benefit. The difference in the succeeding days is less marked, perhaps because pain at this stage is related more to bowel distension than to the incision. One or two patients have complained of slight "stiffness" over the ribs for the first few days, but severe pain or paraesthesiae have been completely absent. A few have noted persistent numbness of the abdominal wall, but in none has it been a symptom of any seriousness or in any way interfered with normal convalescence.

Treatment of Amputation Neuroma

This is a notoriously difficult subject, and the assessment of the efficiency of any method of treatment is so bound up with psychological factors as to be almost impossible. We do not discuss in this paper the relative merits of the various methods of treatment, but merely seek to record the efficacy of the benzocaine-urethane solution in producing local analgesia and pain relief, and to lay down the rules for a satisfactory technique for the benefit of those who seek a long-acting anaesthetic for use in this condition.

One of us (M. V.) has now treated 60 patients by the local injection of benzocaine-urethane solution. A few were patients with painful scars of the extremities, but most of them were amputees. The cases fell into three classes: (1) painful stumps with tender palpable neuromata; (2) stumps with painful adherent scars; and (3) painful stumps associated with phantom pain. All patients had received previous treatment by a variety of methods, in most cases over a period of years. Previous non-operative methods of treatment included physiotherapy, percussion (Russell and Spalding, 1950), and the injection of aqueous local analgesics, while many of the long-standing cases had had repeated surgical treatment—excision of neuromata, excision of scar, and reamputation. A preliminary test injection with 2% procaine was performed in all cases; and no patient was treated with benzocaine-urethane unless substantial relief of pain lasting at least one hour could be secured by the test injection.

The injection itself was carried out under local analgesia in most cases, but a few apprehensive patients received general anaesthesia. Direct injection of the solution either subcutaneously or around a neuroma produces a temporary

burning pain of considerable severity, so that some form of anaesthesia should always be used.

Injection is carried out according to the rules already laid down. Direct injection into the neuroma or nerve trunk is avoided, and the aim of the techniques is to surround the neuroma with a series of small depots placed closely enough to have a confluent action. A large neuroma may thus have as many as 12 or even 20 separate injections (made, of course, without more than one or two actual withdrawals of the needle). The smallest amount of solution used was 1 ml. and the largest 20 ml., and care was taken to avoid depositing more than 1 ml. in any one spot. The only complication seen was occasional mild local swelling and redness at the injection site, which always subsided without specific treatment in from one to three days. In no case did any necrosis, sloughing, or abscess formation develop.

Results

Of the 60 patients treated, 12 failed to gain relief beyond that so often seen after the injection of aqueous procaine. Of these, seven were classed as "predominantly functional" and four actually had, after psychiatric consultation, electric convulsion treatment, also without relief; in two others the pain was later shown to be due to an ill-fitting prosthesis, and was relieved when this was corrected. The remaining 48 all gained worth-while relief of pain. In a few, followed for from six to twenty-four months after the first injection, no further treatment has been necessary. The majority, however, after a period of one to three months, experienced a return of pain: a number of these were so favourably impressed by the result of the first injection that they returned asking for more, and no patient refused a second injection when it was advised. In every case the relief given by the second injection lasted longer than that from the first; and in those patients who again relapsed a third injection gave relief, which has so far been permanent. Detailed analysis and follow-up are not described in this paper, which is concerned primarily with the properties and uses of benzocaine-urethane, and not with a discussion of the treatment of painful stumps. The histories in 10 typical successful cases are summarized in Table II as an indication of the results which may be expected.

TABLE II.—*Histories of 10 Representative Cases of Painful Stump Treated with the Benzocaine-Urethane Solution*

Case	Age	Duration of Symptoms	Previous treatment	Amount Used	Duration of Relief
1	54	10 yrs.	Physiotherapy, percussion	4 ml.	1st injection, 2 months; 2nd, 4 months
2	61	12 yrs.	Physiotherapy, trim of stump	3 "	1st injection, 1 month; 2nd, 6 months
3	34	3 mths.	Physiotherapy	2 "	No recurrence after first injection
4	56	12 yrs.	Physiotherapy, percussion	8 "	1st injection, 1 month; 2nd, 3 months; 3rd, no recurrence
5	53	6 yrs.	Physiotherapy, percussion	5 "	1st injection, 2 months; 2nd, 3 months
6	65	8 yrs.	Physiotherapy, injection	3 "	1st injection, 1 month; 2nd, 2 months; 3rd, 6 months
7	29	10 yrs.	Physiotherapy	4 "	1st injection, 1 month; 2nd, 4 months
8	38	2 yrs.	"	3 "	1st injection 3 months; 2nd, 6 months
9	27	4 yrs.	Excision of neuroma	2 "	No recurrence after first injection
10	35	10 yrs.	Physiotherapy	4 "	1st injection, 1 month; 2nd, 3 months; 3rd, 6 months

In all cases the duration of relief after the last injection continues, and no patient has so far required more than three injections.

Summary

A 2% solution of benzocaine in urethane has been used to produce prolonged local analgesia for the relief of pain after upper abdominal operations, and in the treatment of painful amputation stumps. Other workers have described its use in proctology (Spira, 1946; Rachet *et al.*, 1950), in gynaecology (Dresel, 1949; Arnous and Rey, 1951), and in the relief of pain of rib fractures (Winkler, 1951).

The solution has proved free from the drawbacks and disadvantages affecting all the preparations previously described. It has the great advantages of low viscosity (so that accurate injection is easy without the use of special syringes) and of an almost neutral reaction (and hence freedom from irritant effect and from the tendency to tissue necrosis). A third argument in its favour is that it is easily prepared and sterilized in any hospital dispensary; a quantity sufficient for a full intercostal block costs only a few pence.

This solution is advocated as the best at present available for further experimentation by surgeons interested in the possibilities of prolonged local analgesia.

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ADDENDUM.—Since this paper was written reports have appeared of the toxicity, especially on intravenous injection, of some of the proprietary preparations used for prolonged analgesia. As accidental intravenous injection is always a possibility in performing intercostal block, or in injecting a large nerve, we have had toxicity tests carried out on the benzocaine-urethane solution. Dr. A. C. White, of the Wellcome Research Laboratories, has kindly performed tests which show that in mice, while intravenous injection in a dosage of 2.5 ml. per kg. is uniformly fatal, a dose of 1.25 ml. per kg. can be given to a consecutive series of 10 mice without ill effect. Such a dose is, of course, about one hundred times as great as would be injected in any one site in our technique, and ten times the total dosage needed for a complete bilateral intercostal block. It would seem, therefore, that this is a hazard which need cause no serious concern to users of this solution.

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STELLATE GANGLION BLOCK IN GENERAL PRACTICE

BY

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Anaesthetizing or blocking of the stellate ganglion was originally described 20 years ago, but I can find no evidence to suggest that it has ever been recommended or used as a procedure suitable for the general practitioner. It may be of interest to record that I have performed this operation under normal general practice conditions on 342 occasions on 139 patients.

There seems to be little doubt that the credit for the origination of this procedure must be given to Professor René Leriche. He and Fontaine in 1934 were the first to refer to it. In 1936 he and Fontaine produced a further paper. Neither of these papers was the subject of much comment at the time. In their first paper they published the result of 200 stellate ganglion injections which they had done in the previous nine years, and

stated that stellate ganglion infiltration was not effective unless it was followed by Horner's syndrome and facial vasodilatation.

In 1938 Mackey and Scott described 19 cases of apoplexy which they treated by stellate ganglion block. Of these, nine cases showed improvement. They summarized their results by saying that these did not justify the adoption of anaesthesia of the stellate ganglion as a routine method of treatment in apoplexy, but that further study was necessary before the method was rejected as of negligible value. Nevertheless, as in several of their cases Horner's syndrome was not produced, this cannot be regarded as a fair sample.

Most of my cases are those of hemiplegia due to cerebral thromboses. The attitude of the medical profession towards these has become one of nihilism. This state has arisen for several reasons: (1) There has not been sufficient effort to separate the three major causes—(a) cerebral embolism, (b) cerebral thrombosis, (c) cerebral haemorrhage; (2) it has been thought that cerebral damage is inevitable; (3) some patients have recovered without specific treatment (Gilbert and de Takats, 1948).

A clinical classification of cerebral vascular accidents on an aetiological basis of haemorrhage, thrombosis, or embolism is essential, since a patient suffering from cerebral haemorrhage should not be subjected to stellate block, or at least it should not be done until a long period of observation has indicated that bleeding has ceased (Butt and Mathers, 1948).

From my point of view the most significant symptom in the differential diagnosis between cerebral thrombosis and cerebral haemorrhage is the presence of neck rigidity in cerebral haemorrhage. If neck rigidity is present stellate ganglion block should be avoided. Any theory directed towards relief of a disordered physiological state brought about by cerebral thrombosis can have but one purpose, and that is to restore the blood supply to the specific area of the brain (Volpitto and Risteen, 1943).

Villaret and Cachera (1939) produced cerebral emboli artificially in dogs and watched the vessels of the pia through windows in the skull. These vessels went into spasm even in areas not directly affected by the emboli and persisted thus for some weeks. The sympathetic nerve supply to the cerebral vessels comes from the upper thoracic segments of the spinal cord and passes by way of the stellate and cervical ganglia. If, therefore, these are anaesthetized the cerebral blood flow is increased. Volpitto and Risteen (1943) made two trephine holes into the skull under local analgesia, and the cortex was visualized before and after injection of the stellate ganglion with procaine. They observed that the increase in the calibre of the pial vessels is limited to the affected side. The effect is immediate and does not increase with further time or additional procaine. The scalp and dural vessels become dilated, as do the vessels of the cerebral cortex.

If improvement is to follow a cervical sympathetic block the improvement should be noticed within ten minutes. Should there be a relapse, a further injection should be given (Gilbert and de Takats, 1948).

I have chosen for treatment cases of hemiplegia due to cerebral thrombosis, Raynaud's disease, severe cardiac pain in angina pectoris, and stiff shoulders. I have reported only cases in which there was an actual block of the stellate ganglion, this being shown by the presence of