Effects of regional guanethidine infusion in certain painful states

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SUMMARY Guanethidine was infused by the regional intravenous technique into upper and lower limbs of patients with painful hyperpathic states, due to peripheral or central lesions. The relief of pain and hyperpathia occurred within 20 minutes of infusion and lasted between three and 128 hours; in a few patients, the relief has lasted for months. Great reduction in skin conductance and vasodilatation occurred, there being marked variation in the time of onset and duration of these effects. In some cases there was marked pilo-erection. Guanethidine given in this way did not completely block the sympathetic control of digital blood-vessels. There were no effects on sensibility of normally innervated regions.

In a previous paper, Loh and Nathan1 reported that the chronic painful states that were relieved by blocking the sympathetic outflow were those characterised by the presence of hyperpathia and allodynia.† They concluded that this state of abnormal sensitivity was being maintained by the release of noradrenaline in the neighbourhood of the peripheral nerves. The lesions in the cases were damage to peripheral nerves or nerve roots and, in a few cases, damage within the central nervous system. In the work reported at that time, the sympathetic outflow had been blocked in two ways: by the injection of local anaesthetic solutions into the sympathetic chain and ganglia, and by the infusion of guanethidine intravenously distal to a cuff occluding the circulation, as recommended by Hannington-Kiff.2 The various effects of guanethidine reported at that time were not considered. These actions of guanethidine, given by infusion into upper and lower limbs, are reported here. They are the times of onset and duration of pain relief, vasodilatation, alteration in skin conductance and pilo-erection.

Here we are reporting only cases in which guanethidine removed the pain and hyperpathia. Although this paper is not concerned with this technique as therapy for these cases, it is to be stressed that six out of 30 of the patients have had relief of this state for six months or more.

Patients and methods

Patients with chronic pain were selected on the basis of having allodynia and cutaneous hyperpathia; some also had deep hyperpathia. The numbers of patients and their diagnoses are shown in table 1. Of these 30 patients, one had four blocks given within a period of four weeks.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral nerve lesion</td>
<td>6</td>
</tr>
<tr>
<td>Reflex sympathetic dystrophy</td>
<td>5</td>
</tr>
<tr>
<td>Compression of nerve or nerve roots</td>
<td>4</td>
</tr>
<tr>
<td>Sudeck's atrophy</td>
<td>2</td>
</tr>
<tr>
<td>Spinal cord lesion</td>
<td>2</td>
</tr>
<tr>
<td>Painful legs and moving toes (3)</td>
<td>2</td>
</tr>
<tr>
<td>Causalgia</td>
<td>1</td>
</tr>
<tr>
<td>Unclassified disorder of sympathetic system</td>
<td>1</td>
</tr>
<tr>
<td>Pathological vascular state of periphery of limb</td>
<td>1</td>
</tr>
<tr>
<td>Amputation stump</td>
<td>1</td>
</tr>
<tr>
<td>Carcinomatous invasion of brachial plexus</td>
<td>1</td>
</tr>
<tr>
<td>Arachnoiditis</td>
<td>1</td>
</tr>
<tr>
<td>Pain following removal of two herniated lumbar discs</td>
<td>1</td>
</tr>
<tr>
<td>Midbrain injury due to closed head injury</td>
<td>1</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>2</td>
</tr>
<tr>
<td><strong>TOTAL:</strong></td>
<td><strong>30</strong></td>
</tr>
</tbody>
</table>

*Member of the External Scientific Staff, Medical Research Council.
†The terms used are those recommended by the International Association for the Study of Pain. Hyperpathia is "a painful syndrome, characterised by delay, over-reaction and after-sensation to a stimulus, especially a repetitive stimulus." Allodynia is a state in which pain is caused by a stimulus which does not cause pain in normal skin.

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and four had two blocks given within a period of a week. Only patients in whom pain, hyperpathia and allodynia were removed by the infusion of guanethidine are presented here.

**Guanethidine given by Bier’s block**
The limb was elevated for about a minute to empty the veins. A Kidde automatic tourniquet was put on the arm or thigh, inflated to a pressure above systolic blood pressure and maintained for 20 to 25 minutes. Guanethidine monosulphate in isotonic saline was injected into a vein of the hand or foot two minutes after occlusion of the circulation. The dose was 10 to 15 mg in 20 ml of saline for the upper limb and 15 to 20 mg in 40 ml of saline for the lower limb. On one occasion 1·5 mg of guanethidine was given in 30 ml of saline to an upper limb.

There were no general effects from the guanethidine on release of the cuff, except in one patient. On one of the two occasions when the cuff was removed, she had abdominal pain felt in the region where she had had pain with cholecystitis.

**Control procedures for the relief of pain and hyperpathia by guanethidine**
It was necessary to know that, under the conditions of infusion guanethidine, the relief of pain, hyperpathia and allodynia were not due to a local anaesthetic action of guanethidine nor to the occlusion of the circulation.

(a) As guanethidine has local anaesthetic activity, local anaesthetic solutions were given on a few occasions by the same technique. Lignocaine 20 ml of 0·5 per cent solution were given. Within three minutes of deflation of the cuff, the analgesia had passed off and the pain and hyperpathia had returned.

(b) In two of the patients of this series and in many others with hyperpathia and allodynia, occlusion of the circulation was carried out for 25 minutes without administering guanethidine. This sometimes relieved the condition for one hour but never for longer periods.

**Sensory effects**
Patients were tested by applying those stimuli that were most painful and produced the particular quality of pain of which the patient complained. Pain was also examined by pinprick to the skin and by squeezing the deep tissues. Touch was examined by stroking and rubbing.

**Digit temperature**
The temperature of the digits and interdigital webs was measured with thermocouples or mercury skin thermometers. Skin temperature was taken to assess dilatation of digital blood vessels.

**Digit plethysmography**
The neural control of the blood vessels of the fingers or toes was examined by mercury strain gauge loops round the digits. The signal was amplified and recorded on an ink-writing recorder. In order to induce a sympathetic response, the following manoeuvres were employed: Valsalva manoeuvre, hand-grip on a dynamometer, an evaporating cooling solution sprayed on face or neck; sudden auditory shock such as banging a door; mental arithmetic; repeated pinprick or other painful stimuli in the locally painful area.

The tests for vasodilatation, for control of skin vessels of the digits, and for conductance were not performed after all blocks. The reasons for this were that it was only after we had done several blocks for therapeutic purposes that we noticed the large variation in the different effects of guanethidine; and so at first the various tests were done only infrequently. The other reason was that with heated hospital wards, there was usually full vasodilatation of the control, untreated limbs, and so any dilatation of the treated limb could not necessarily be attributed to guanethidine.

**Electrical conductance through the skin**
Skin resistance increases, and thus conductance decreases, with decreasing sympathetic activity. The theoretical basis and the factors determining conductance have been investigated by Woolley-Hart. Skin resistance was measured by an ammeter (Relaxation Meter, Medici). Changes in current were measured by applying a constant voltage. Two types of electrode were used, one for the palm or sole and one for the digits. The electrode diameter was 1·5 cm. The distance between palm or sole electrodes was 3·5 cm. The digit electrodes were mounted independently on Velcro strapping. The voltage was adjusted to produce a current of either 25 μA or 50 μA in the control limb or in the affected limb before injecting the guanethidine. Any change in current indicated a change in conductance.

**Results**

**Relief of pain, hyperpathia and allodynia**
Pain, hyperpathia and allodynia were relieved within 18–23 minutes of the injection. Deep
tenderness was less affected. The relief of hyperpathia often came on while the guanethidine was causing severe burning pain. There was no effect on sensibility except for the removal of hyperpathia and allodynia; and there was no effect on normally innervated areas. For instance, in a case with a lesion of the median nerve, the injection of guanethidine removed the abnormal sensitivity from the median territory and had no effects in the ulnar territory.

The relief of the pain occurred while the cuff was still on in 22 blocks and on removal of the cuff in the remaining 15 blocks. It is thought that there is no difference between these two populations, for those who did not notice relief of pain and hyperpathia until the cuff had been removed were probably too preoccupied with the various sensations and discomfort from having a tight cuff on the limb to notice any change in the underlying pain. The duration of relief of pain and hyperpathia and allodynia is shown in Table 2. In 24 out of 37 of the blocks, the relief lasted for less than 24 hours; in six patients it has lasted for more than six months. From a therapeutic point of view, these results appear to be rather unsatisfactory. They are more so when one remembers that we are discussing here only the patients in whom guanethidine relieved pain and hyperpathia. We have seen at least a further ten patients in whom it failed to do so.

The injection in one patient of a tenth of the usual dose (1.5 mg) had some slight effects in relieving the sensitivity to stimulation but no other effects.

Vasodilatation and neural control of digital blood vessels

Reactive hyperaemia following removal of the cuff was slight, usually raising the digital temperature by only 2°C.

The time of onset of vasodilatation due to the infusion of guanethidine is shown in Table 3. Vasodilatation started to occur on removal of the cuff in four blocks; in Table 3, this is called "immediate". The range of time of onset of vasodilatation was wide, between 20 minutes and 24 hours. This is, however, a somewhat arbitrary figure as it took around one hour for full vasodilatation to occur.

The duration of vasodilatation is shown in Table 4. In most blocks this was for at least 48 hours. This is an arbitrary figure for the time between full vasodilatation and return to the temperature before guanethidine was usually about 24 hours. By the times given in the table, the temperature of the two hands or two feet was the same. To be sure that there was full return of vascular tone, it would have been necessary to put the patients in a cold environment to see if vasoconstruction was equal in the two limbs. This was not done.

Tests of sympathetic control of the peripheral blood vessels showed complete block of sympathetic nerves in only one case. In all others, a partial block was shown by the fact that some manoeuvres still caused vasoconstriction. Partial block was shown within two hours of the infusion of guanethidine in four, between two and three hours in one, by four hours in one, and around 5.5 hours in one. Further evidence that vasodilatation was incomplete was obtained on two occasions by blocking the ulnar and median nerves with local anaesthetic solution during the time of the vasodilatation induced by guanethidine. In both cases, the local anaesthetic block produced a slight, further rise in digital temperature. Thus guanethidine did not completely block sympathetic control of the blood vessels of the digits. This is unlikely to have been due to an insufficient dose, as the same block occurred with 15 mg as with 30 mg.

Guanethidine often produced effects that could have been attributed to histamine release, such as engorgement of the tissues, slight oedema and itching.

Skin conductance

The effects of occluding the circulation on conductance need to be considered. Edelberg6 found that during the time of occlusion conductance usually stopped, and when the circulation was restored conductance returned to its previous, or to a higher, level. In our cases, conductance

<table>
<thead>
<tr>
<th>Number of blocks</th>
<th>1 d</th>
<th>2 d</th>
<th>3 d</th>
<th>4 d</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>8</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>
Effects of regional guanethidine infusion in certain painful states

449

went down to zero with the current used when the cuff was on, and continued to remain so on removal of the cuff in eight blocks. After four blocks, conductance returned to its previous level on removal of the cuff, and remained at that level or two hours. After one block, it increased when the cuff was removed. It was unrecordable within two hours in one block, within three hours in one block, and within four hours in one block. We have insufficient evidence on the duration of reduction of conductance.

We did not undertake a study of sweating; for sweating, being cholinergic, was not expected to be affected by guanethidine. However, we observed that in limbs into which guanethidine had been injected, sweating was sometimes present and sometimes absent.

Pilo-erection

An unexpected finding was marked erection of the arrectores pili muscles in the part treated by guanethidine. An example is illustrated in fig 1. It occurred in about a third of the trials. It came on while the cuff was still on in two blocks in one patient, and immediately the cuff was removed in six patients. At these times, vasodilatation had not yet occurred. In four of these patients it lasted up to 24 hours and in one, it lasted eight hours.

Times of onset and duration of various effects

It is clear that the onset and duration of various effects of guanethidine infusion vary considerably. The pain and hyperpathia are always removed either while the cuff is still on or immediately it is released. At this time there is no block of sympathetic activity as judged by skin conductance, and in most cases vasodilatation had not started to occur. The lack of relationship between relief of pain and onset and duration of vasodilatation was strikingly demonstrated in two patients in whom pain and hyperpathia returned within the period of vasodilatation; a second infusion of guanethidine given during this period had the same therapeutic effect as the first, the relief of pain and hyperpathia lasting between 12 and 36 hours.

There was no relation between reduction in conductance and vasodilatation. Reduction of conductance sometimes occurred before vasodilatation; it often occurred as vasodilatation developed. It returned to its normal level while the vasodilatation continued.

Discussion

Preventing sympathetic activity by injecting local anaesthetic solutions into the chain and ganglia stops the pain, hyperpathia and allodynia, reduces conductance to a minimum, and causes vasodilatation; these effects occur at the same time. The local infusion of guanethidine has the same effects but they are spread out in time.

The action of guanethidine is to release noradrenaline and then to prevent re-uptake and thus to deplete it at noradrenergic varicosities, according to Chang et al.7

Pain

In considering how guanethidine relieves certain hyperpathic states, one must first exclude any local anaesthetic action of the substance. The following points would seem to remove this possibility: (a) in the control cases in which

Figure Pilo-erection in left upper limb following infusion of guanethidine. Note the sharp border at the lower level of the cuff.
lignocaine or bupivacaine was injected, the removal of hyperpathia and pain lasted only three minutes after removal of the cuff; (b) guanethidine has no effects on the sensitivity of normally innervated areas below the cuff; (c) anaesthesia is not found over the cornea when 5% guanethidine eyedrops are used; (d) if a local anaesthetic effect were occurring in our material, the small sympathetic fibres would have been blocked immediately. But in the majority of our trials this was not so.

Why in some lesions of the nervous system, blocking the sympathetic nerve fibres stops the abnormal sensitivity and pain is unknown. It is proposed that in the cases with hyperpathia and allodynia, peripheral nerve fibres have become abnormal in that they have become sensitive to adrenaline and noradrenaline. This suggestion is based on experiments carried out by Wall and Gutnick on nerve fibres in a neurona induced on the cut sciatic nerve of the rat. After a certain time, some of the afferent myelinated fibres started firing spontaneously. Noradrenaline and adrenaline increased their firing rate and activated these fibres when they were quiet. This activity was stopped by alpha and beta blockers.

It seems to be that if there is a lesion anywhere along an afferent pathway—in the thalamus, in the midbrain, within the spinal cord, in the posterior nerve roots or in the peripheral nerves—the peripheral nerve fibres may become abnormal. They are abnormal in that they become sensitive to mechanical distortion, liable to discharge impulses frequently and spontaneously, and abnormally sensitive to noradrenaline and adrenaline. We do not know when noradrenaline stores would have been depleted following guanethidine given by Bier's block. Data from investigations of other situations in species other than man provide us with no evidence. It is likely that at the time when the spontaneous pain and hyperpathia had been removed, the presumed firing of somatic afferent nerve fibres as a result of the effect of noradrenaline had ceased. Yet at that time, the sympathetic terminals would probably not have been depleted of transmitters.

Skin conductance
Skin conductance was examined as it is another measure of sympathetic activity. The times of onset of reduced conductance do not fit with what is known about times of depletion of noradrenaline. Conductance was so low that it could not be measured after eight blocks on removal of the cuff, but after nine blocks it returned to its previous level, and started to diminish after two hours. Depletion of noradrenaline is said to occur in two hours and become fairly complete within 18 hours.

Vasodilatation
When the sympathetic chain is blocked by local anaesthetic solution, the immediate effect is vasodilatation; it lasts between two and four hours, and the skin vessels do not respond to manoeuvres inducing sympathetic excitation. With guanethidine, however, the effect is progressive. In a minority of trials, vasodilatation started to occur on removal of the cuff; in the rest it came on at any time between 1.5 and six hours. From the time when the digital temperature exceeded that of the control limb to full vasodilatation took around one hour. It lasted from one to four days, and during this period the vessels could be slightly constricted by induced sympathetic activity. Sympathetic activity, as judged by skin conductance, had returned to normal within 20 hours; but vasodilatation usually continued up to about four days. Sweating was sometimes obvious at a time when there was full vasodilatation. It is therefore seen from these observations that vasodilatation continued long after the expected period of noradrenaline depletion. Thus it appears that the vasodilatation following guanethidine cannot be due only to sympathetic blockade. There is evidence that guanethidine can have a direct action on the blood vessels. After depletion of noradrenaline stores by reserpine, guanethidine still causes a fall in blood pressure. Abboud and Eckstein gave guanethidine intra-arterially to dogs that had previously been treated with reserpine or in which the limbs into which the guanethidine was injected had been denervated. They concluded that guanethidine "had a direct vasodilator action on the blood vessels of the dog's denervated leg" directly affecting the vascular smooth muscle. This effect did not appear to be mediated through the release of catecholamines, histamine or acetylcholine. Angus et al. also noted the duration of vasodilatation after guanethidine and tried to determine whether it could be due to autonomic blockade. From an examination of hindlimb blood flow and vascular resistance in the rabbit, they too concluded that "most of the vasodilatation following guanethidine is not mediated by the autonomic nervous system". However, they thought it was due to histamine release, although they admitted that, in spite of their positive evidence, the vasodilatation...
Effects of regional guanethidine infusion in certain states

was not influenced by H₁ and H₂ antagonists. Cooper et al.⁵ injected guanethidine intra-arterially into the upper limbs of man. They injected 5 mg in five minutes, a smaller dose than we used. They used one of the tests we used for causing vasoconstriction, ice applied to the neck. There was immediate vasoconstriction, which lasted for 30 minutes. Maximal vasodilatation was present at five hours and lasted for 20 hours. Judging by the response to the ice, they concluded that it took 30 minutes for the sympathetic control of the distal vessels to become complete. They concluded that “most of the vasodilatation following guanethidine is not mediated by the autonomic nervous system,” and they thought it was related to the release of histamine.

Pilo-erection
In some of our cases there was a prominent excitation of the arrectores pilorum of the limb. Guanethidine has no direct action on these muscles; this was shown by Hellman¹⁴ in an excellent study of the pilomotor muscles of rats, mice, guinea pigs and cats. The innervation of the muscles was shown to be “wholly adrenergic.” After giving bretylium or guanethidine, electric stimulation failed to excite the muscles; they remained sensitive to adrenaline and noradrenaline; indeed, bretylium increased the response to adrenaline though not to noradrenaline. Whether the early pilo-erection is due to the release of noradrenaline by guanethidine is not known.

Conclusions
In view of the different effects of guanethidine infusion to a limb occurring at such different times, any general conclusions must be only tentative. The hyperpathia and pain were always stopped within minutes. Full blocking of sympathetic control of digital blood vessels did not occur. The prolonged vasodilatation may not be due to sympathetic nerve blockade but to other mechanisms.

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References