Treatment of painful diabetic neuropathy

Introduction

The treatment of painful neuropathy is always difficult as the cause of this distressing complication of diabetes is not fully known. The overall strategy of management is based on the premise that the duration of the severest pain is usually limited to 2 years at most (Archer et al, 1983). Throughout this time, therefore, it is necessary to support the patient with painful neuropathy, using various symptomatic treatments which, by trial and error, are found to benefit the patient. It should be appreciated that with each therapy there is often a clear placebo effect.

It is important to explain the symptoms and management of painful neuropathy to the patient and this is fundamental for successful management (Watkins et al, 1996). The most severe and unpleasant symptoms of painful neuropathy resolve in 6–8 months, but may occasionally last for up to 2 years. Symptoms may disappear completely and leave no residual signs.

When the symptoms are less severe, some discomfort and paraesthaesia may persist for years, although normal body weight is always restored. Relapses are very uncommon.

Reassurance that painful neuropathy will neither cripple the patient nor result in amputations, and that the severe symptoms will eventually remit, are important aspects of the approach to the patient with painful neuropathy. It is necessary to explain that the intensity of discomfort is likely to vary considerably and may be related to other stressful factors in the patient's life.

Many patients complain that the severity and intensity of their pain is not fully appreciated, and it is essential for healthcare professionals to show a genuine respect and concern for the patient's symptoms (Young, 1997).

DIABETIC CONTROL

Diabetic control should be optimal, using insulin if necessary. It would seem sensible to optimise diabetic control, as a period of poor glycaemic control can lead to acute painful neuropathy.

The Diabetes Control and Complications Trial (DCCT Research Group, 1993) has firmly established that tight glycaemic control will significantly reduce the risk of developing neuropathy in patients with type 1 diabetes mellitus. Thus it is important to optimise glycaemic control, even in those in whom painful neuropathy is precipitated by the onset of tight control (Llewelyn et al, 1986).

This is not an indication to relax blood glucose control. Continuous subcutaneous insulin infusions have been shown to be beneficial in patients with severe neuropathy (Boulton et al, 1982).

SIMPLE ANALGESICS AND HYPNOTICS

Regular analgesics are essential in the treatment of painful neuropathy, starting with simple analgesics such as aspirin, paracetamol and mild opiates (e.g. dextropropoxyphene) or combinations of these.

It is best to avoid drugs that may lead to addiction, except possibly to promote sleep when the symptoms are most severe. Sleep can easily be disturbed by the exacerbation of neuropathic pain at night in bed, so that it is important to prescribe hypnotics, often early in the disease, to maintain sleep and improve the patient's morale.

TRICYCLIC ANTIDEPRESSANTS

Tricyclic antidepressants block presynaptic reuptake of serotonin and noradrenaline. In animal studies, an increase in serotonin in the synaptic cleft has been associated with an increase in the pain threshold.

Controlled trials have established that tricyclic antidepressant drugs are useful in alleviating painful neuropathy (Low and Nelson, 1996). However, a reduction in severity rather than total abolition of pain is usually achieved (McQuay et al, 1996).

Both burning pain and

1 CURRENT TREATMENT OF PAINFUL DIABETIC NEUROPATHY IS UNSATISFACTORY.

2 SEVERE PAIN DOES NOT USUALLY LAST MORE THAN 2 YEARS AT THE MOST.

3 IT IS ESSENTIAL TO PROVIDE COMFORT, SUPPORT AND REASSURANCE TO PATIENTS THROUGH THE PAINFUL PHASE.

4 PAIN RELIEF MAY BE ACHIEVED WITH DRUG THERAPY, EITHER ALONE OR IN COMBINATION WITH PHYSICAL MEASURES.

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lancinating pain are relieved by tricyclic anti-depressant agents. It is important to watch out for side-effects, particularly postural hypotension and gastrointestinal and bladder symptoms.

The tricyclic antidepressants commonly used to control burning neuropathic pain are imipramine, amitriptyline and desipramine.

Imipramine can be a useful agent with which to commence therapy. It is slightly less efficacious than amitriptyline, but has fewer side-effects. It is advisable to commence treatment at a low dosage and to increase the dose gradually, depending on the symptomatic response. Thus, with imipramine it is best to commence treatment with 25–50 mg at night, increasing by 25 mg increments on alternate days.

Imipramine is best taken at night because of its action in relieving nocturnal neuropathic pain as well as its sedative action. The addition of a phenothiazine, such as fluphenazine, enhances the analgesic effect but may make the postural hypotension worse (Young, 1997).

Reuptake of both serotonin and noradrenaline is important for the inhibition of pain in painful diabetic neuropathy. Other anti-depressant drugs such as mianserin, which do not block neurotransmitter uptake, and fluoxetine, which inhibits serotonin reuptake, do not normally cause significant pain relief (Max et al, 1992).

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

Citalopram, paroxetine and other selective serotonin reuptake inhibitors are just as effective in providing analgesia as imipramine (Sindrup et al, 1990, 1992). Paroxetine and citalopram alleviated painful symptoms, while fluoxetine only relieved pain if there was accompanying depression.

It has been suggested that nefazodone, a serotonin reuptake inhibitor, or venlafaxine, a serotonin/noradrenaline reuptake inhibitor, might be better tolerated than tricyclic antidepressants, but no controlled trials are available.

ANTICONVULSANT DRUGS

Anticonvulsant drugs have an established role in the treatment of painful neuropathy (McQuay et al, 1995). They act by stabilising neuronal membranes through an effect on sodium conductance.

Carbamazepine, valproate and phenytoin have been used to relieve neuropathic pain.

Clinically, carbamazepine seems to be the most useful. It can be started at 100 mg once or twice daily, and then be increased up to the maximum tolerated dosage (usually 800–1000 mg/day).

Valproate (100–500 mg one to three times daily) and phenytoin (100–400 mg once or twice daily) are useful alternatives.

Recently, newer anticonvulsants such as gabapentin and lamotrigine have been recommended. A recent randomised controlled study by Backonja et al (1998) found that gabapentin significantly reduced the painful symptoms as well as improving sleep.

ANTI-ARRHYTHMIC DRUGS

The membrane stabilising drugs lignocaine and mexiletine have both been reported to be effective in relieving painful diabetic neuropathy. Lignocaine has to be given by intermittent intravenous infusion and may provide pain relief for several days.

In a double-blind trial of oral mexiletine, patients with stabbing or burning pain reported definite alleviation of pain (Stracke et al, 1992).

Mexiletine often has unacceptable side-effects, although dosages of 450 mg per day significantly reduced lancinating and burning pain and paraesthesia without causing cardiovascular side-effects.

Table 1. Treatment options for painful diabetic neuropathy

Glycaemic control

Tricyclic antidepressant drugs
- Amitriptyline
- Imipramine
- Clomipramine
- Desipramine

Selective serotonin reuptake inhibitors
- Paroxetine
- Citalopram
- Fluoxetine

Anticonvulsant and antiarrhythmic drugs
- Phenytoin, carbamazepine, gabapentin, lamotrigine, mexiletine, lignocaine
- Transdermal clonidine, prostacyclin analogues

Topical capsaicin

Physical measures
- Transcutaneous electrical nerve stimulation
- Opsite film
- Electrical spinal cord stimulation

CAPSAICIN

Capsaicin induces the release of various peptide neurotransmitters from nerve endings, leading to depletion of the peptides in nerve terminals and failure of transmission at the synapse.

One of the peptides released is substance P, a peptide neuro-transmitter involved in pain transmission at various levels (Young, 1997). The acute release of substance P often causes transient burning or stinging; this is followed by insensitivity to painful thermal or mechanical stimuli which lasts several hours.

Capsaicin cream should be applied sparingly in a thin layer, three or preferably four times a day to the affected areas. Topical capsaicin can give rise to local stinging and burning, but these effects are often transient and disappear if the cream is applied regularly. Patients should be encouraged to persist with treatment until this passes — usually within 2 weeks, although it can occasionally take up to 6 weeks. The analgesic effect may take up to 6 weeks to develop (Young, 1998).

In patients with diabetic neuropathy, trials of capsaicin cream (0.075%), applied to the skin of the foot, have demonstrated significant reductions in pain intensity, especially of burning pain (Scheffler et al, 1991; Capsaicin Study Group, 1991, 1992; Tandan et al, 1992).

In the last 5 years, several studies have compared the effects of capsaicin cream and the vehicle in which it is formulated (Scheffler et al, 1991; Tandan et al, 1992; Biesbroeck et al, 1995). They have reported a significant benefit in favour of capsaicin.

Biesbroeck et al (1995) compared the effects of topical capsaicin with amitriptyline in painful diabetic neuropathy. Capsaicin and amitriptyline produced equally good pain relief, with a mean pain reduction of 40%.

Since topical capsaicin penetrates only the subdermal layer, it has been considered ideal for the treatment of neuropathic pain. It has no serious systemic side-effects. Initial concerns that it might predispose the user to worsening neuropathic damage seem unfounded as thermal threshold and vibration thresholds remain unchanged after the use of capsaicin cream.

PHYSICAL METHODS

Transcutaneous electrical nerve stimulation (TENS) machines are battery-powered electrical devices that deliver a low voltage electrical stimulation to the sites of painful neuropathy. This blocks the transmission of pain impulses, and may encourage the release of endorphins.

Painful symptoms include burning or lancinating pain, painful paraesthesia, contact discomfort, restless legs and cramps

Electrodes are placed on either side of the painful area and the settings on the machine are adjusted until a pleasant tingling sensation is felt across the area of the pain.

Spinal cord stimulation is carried out with specially developed electrodes placed adjacent to the spinal cord. A recent study of the use of electrical stimulation reported benefit in eight of 10 cases, and it was recommended that this form of treatment should be used in patients who have failed to respond to any conventional methods (Tesfaye et al, 1996).

OPSITE FILM

The application of Opsite, a semi-permeable adhesive film dressing, has been shown to alleviate the pain associated with a chronic painful neuropathy (Foster et al, 1994).

ALDOSE REDUCTASE INHIBITORS

Aldose reductase inhibitors were introduced to prevent the accumulation of sorbitol in nerve.

In an early open study on patients with severely painful diabetic neuropathy, there was a reported benefit with sorbinol. However, this drug was later withdrawn because of side-effects (Jaspan et al, 1983).

Studies with tolrestat indicated a significant improvement in pain scores in favour of the drug (Santiago et al, 1993), but this drug has also been withdrawn because of side-effects.

Further studies with aldose reductase inhibitors are required.

CONTROL OF PAINFUL SYMPTOMS

Painful symptoms include burning or lancinating pain, painful paraesthesia, contact discomfort, restless legs and cramps (Young, 1997; Pfeifer et al, 1993). It is advisable to focus treatment on the dominant unpleasant symptom.

BURNING PAIN

Tricyclic antidepressants such as imipramine, amitriptyline and desipramine

are the drugs that are most effective in controlling burning, neuropathic pain.

Capsaicin can also be used to treat this type of neuropathic pain.

LANCINATING PAIN

Lancinating (resembling an electric shock) pain generally responds to anticonvulsant drugs or membrane stabilising drugs such as lignocaine or its orally active analogue mexiletine.

CONTACT DISCOMFORT

Contact discomfort often accompanies burning pain. It is exceedingly distressing and is precipitated by light contact, e.g bedclothes.

This symptom generally responds to a mechanical approach, such as a bed cradle, and careful choice of clothing worn next to the skin, or the application of a protective mechanical barrier such as Opsite.

PAINFUL PARAESTHESIAE

Tricyclic antidepressant drugs or anticonvulsants may be tried. They are less effective in relieving this symptom than in the relief of burning pain.

RESTLESS LEGS

This very distressing symptom may be the dominant complaint or may coexist with other features, and can seriously disturb sleep.

Clonazepam, a benzodiazepine anticonvulsant, taken at a low dosage of 0.5–1 mg usually provides effective symptom relief.

CRAMPS

Unpleasant cramps may be the only symptom of diabetic neuropathy, but commonly affect older people. Cramps may be caused by muscle denervation or be related to poor diabetic control and electrolyte imbalance.

Quinine sulphate is usually the most effective treatment, although severe and resistant cramps may require a combination of counter-irritant therapies, including TENS.

CONCLUSION

Despite recent progress in our understanding of the mechanisms of painful diabetic neuropathy (Thomas, 1999), current management of the condition is still not satisfactory.

It is most important to provide comfort, support and reassurance to patients through the most painful phase of the condition, using pharmacological and physical measures to alleviate the pain as best possible until remission of the most severe pain occurs. ■

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