Pain management in diabetic neuropathy: Ten years of progress?

Andrew Boulton is Professor of Medicine, University of Manchester and University of Miami, US.

In the late 19th century, Pavy (1885) vividly described the pain of diabetic neuropathy as being 'of a burning and unremitting character'. Approximately 100 years later an editorial in the *Lancet* questioned, 'Can we do anything about diabetic neuropathy or do we just have to document it and commiserate with the patient?' (The Lancet, 1983). Fortunately, many advances have been made in the symptomatic management of painful diabetic neuropathy since that 1983 editorial: this brief review will cover advances over the last 10 years.

Pharmacological agents

There are 2 groups of drugs that can be used in the management of diabetic neuropathy. Firstly, the disease-modifying agents which remain mostly experimental, and secondly there are the symptomatic treatments that might alleviate the pain but are unlikely to affect the natural history of diabetic neuropathy which is that of progressive loss of nerve fibres. It is unfortunate that during the last decade, two potential disease-modifying therapies that might have benefitted people with symptoms have been withdrawn from further development: namely, the PKC-ß inhibitors and no-growth factors.

The only disease-modifying agent that is still under investigation, and indeed used in certain European countries, is the antioxidant alpha-lipoic acid. A meta-analysis of several randomised controlled trials using this agent intravenously has confirmed their efficacy (Ziegler et al, 2004). However, the results of definitive long-term trials are still awaited and should be available in 2008.

Turning now to symptomatic treatments, the first step in the management of painful neuropathy should always be to try and obtain stable glycaemic control avoiding severe fluctuations of blood glucose where possible. Although a number of studies have confirmed a major contribution of prolonged hyperglycaemia in the pathogenesis of neuropathy and pain, there are no controlled studies that have suggested that stable near normoglycaemia is beneficial in reducing painful symptoms. Previous suggestions that blood glucose flux contributes to the severity of neuropathic pain are supported by the observations of Oyibo and colleagues confirming that those with painful neuropathy have more blood glucose instability than those with painless neuropathy (Oyibo et al, 2002).

With regard to the pharmacological management of symptoms, a number of newer agents have been confirmed to be efficacious in this area over the last decade. The original references to trials of the following agents can be found in the 2004 technical review (Boulton et al, 2004). Gabapentin, a drug used in the management of complex partial seizures, has been confirmed as efficacious in painful neuropathy in a number of trials. This drug has to be given 3 times daily, and in clinical practice is often given at too low a dose: the mean dose in the trials was approximately 1.8g per day. More recently, pregabalin, which is structurally related to gabapentin, has proved to be a useful addition to agents used in pain in the relief of painful symptoms. This drug can be given twice daily and is now widely used in the management of neuropathy in the UK. The 5-hydroxytryptamine and norepinephrine re-uptake inhibitor duloxetine has both analgesic and anti-depressant properties and is licensed in the UK for the management of neuropathic pain. Initial experience suggests that this is also another useful addition to the agents used in this condition.

Endocrinologists have been rather reluctant in past years to consider the use of opioid agents in the management of neuropathic pain. However, a number of recent studies suggest that these can be useful in those patients who fail to respond

PAIN MANAGEMENT

Supported by an unrestricted educational grant from

Pfizer

to the agents already listed. Tramadol is a synthetic opioid which has proven efficacy and may be useful for at least 6 months of pain relief (Boulton et al, 2004). Other agents with confirmed efficacy include oxycodone controlled release (Boulton et al, 2004) and there is some open-label evidence to suggest that even methadone might be used in resistant cases (Hays et al, 2005).

To date there have been few comparative studies between different agents for neuropathy but it has been suggested that the combination of gabapentin and morphine might be particularly helpful for helping severe neuropathic pain that is resistant to other therapies. Gilron et al (2005) showed that when combined, these agents achieved better analgesia at lower doses of each drug than either did as monotherapy.

Non-pharmacological therapies

Finally, there is some evidence to support the use of other physical and topical therapies. These include the use of topical glyceryl trinitrate applied locally to the feet (Krishnan and Rayman, 2003), and even acupuncture (Boulton et al, 2004). However, despite there being some initial enthusiasm for other treatments such as electrical therapy and the use of monochromatic infra-red light, recent controlled-trials have failed to support earlier findings. The question of surgical decompression of multiple peripheral nerves and its use in pain neuropathy was the subject of a recent commentary in *Diabetes Care* (Cornblath et al, 2007): the conclusion was that there is no controlled-trial evidence to support the use of this invasive therapy (Chaudhry et al, 2006).

The future

Looking to the future, although there are a number of potential treatments for symptomatic neuropathy in phase 3 trials, it may be some time before disease-modifying agents become available. The development of such treatments may further be hampered because the rate of progression of established diabetic neuropathy may not be as fast as previously believed (Boulton, 2007). It is therefore vital that appropriate surrogate markers for progression of neuropathy are used in such trials; and new treatments will likely include gene therapy. ■

Boulton AJ, Malik RA, Arezzo JS, Sosenko JM (2004) Diabetic somatic neuropathies. *Diabetes Care* **27**: 1458–86

Boulton AJ (2007) Whither clinical research in diabetic sensorimotor peripheral neuropathy? Problems of end point selection for clinical trials. *Diabetes Care* **30**: 2752–3

Chaudhry V, Stevens JC, Kincaid J, So YT (2006) Practice Advisory: utility of surgical decompression for treatment of diabetic neuropathy: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* **66**: 1805–8

Cornblath DR, Vinik AI, Feldman E et al (2007) Surgical decompression for diabetic sensorimotor polyneuropathy. *Diabetes Care* **30**: 421–2

Gilron I, Bailey JM, Tu Det al (2005) Morphine, gabapentin or their combination for neuropathic pain. *NEJM* **31**: 1324–34

Hays L, Reid C, Doran M, Geary K (2005) Use of methadone for the treatment of diabetic neuropathy. *Diabetes Care* **28**: 485–7

Krishnan ST, Rayman G (2003) New treatments for diabetic neuropathy: symptomatic treatments. *Current Diabetes Reports* **3**: 459–67

Lancet, The (1983) Diabetic neuropathy--where are we now? *Lancet* **1**: 1366–7

Oyibo S, Prasad YD, Jackson NJ et al (2002) The relationship between blood glucose excursions and painful diabetic peripheral neuropathy: a pilot study. Diabetic Medicine 19: 870–3

Pavy FW (1885) Introductory address to the discussion on the clinical aspect of glycosuria. *Lancet* **ii**:1085–87

Ziegler D, Nowak H, Kempler P et al (2004) Treatment of symptomatic diabetic polyneuropathy with the anti-oxidant alpha-lipoic acid: a meta-analysis. *Diabetic Medicine* **21**: 114–21