

PERIPHERAL DIABETIC NEUROPATHY: CURRENT CONCEPTS IN TREATMENT

Piera T Calissi and Linda A Jaber

OBJECTIVE: To review pathophysiology and current concepts in the treatment of diabetic peripheral neuropathy (PN).

DATA SOURCES: References were identified through a MEDLINE search of the English-language literature from 1976 through 1994. Additional references were obtained from reference lists of articles identified through the search.

STUDY SELECTION AND DATA EXTRACTION: All articles were considered for possible inclusion in the review. Clinical trials that involved an adequate number of patients and review articles were selected. Information from articles that was judged by the authors to be significant was selected for discussion.

DATA SYNTHESIS: PN affects 5–50% of people with diabetes in the US and most commonly is characterized by tingling or burning sensations, particularly in the calves, ankles, and feet, with a loss of vibratory sense. Treatment of PN, for the most part, has been unsatisfactory. Therapy has been directed toward either improving nerve function or alleviating symptoms of PN, including pain and paresthesia. Glycemic control may slow the progression of PN. Hyperglycemia also is associated with decreased pain threshold in patients with diabetes mellitus. The aldose reductase inhibitors, particularly tolrestat, have been shown to improve objective and subjective neurologic function. Pain or paresthesia has been treated effectively with antidepressants, lidocaine, mexiletine, and capsaicin. The anticonvulsants phenytoin and carbamazepine may be effective, but are associated with a greater degree of adverse effects. Experimental treatments, such as gamma-linolenic acid, gangliosides, uridine, and the corticotropin_{4,9} analog ORG 2766, have been effective in improving neurologic function.

CONCLUSIONS: Treatment of PN remains unsatisfactory. Therapy should be directed toward prevention with glycemic control and symptomatic treatment of existing PN.

Ann Pharmacother 1995;29:769-77.

PERIPHERAL NEUROPATHY (PN) AFFECTS 5–50% of people with diabetes mellitus in the US.¹ The wide range in prevalence reflects the lack of agreement in a standard definition of PN.^{2,3} Factors contributing to a lack of a clear definition of PN include an absence of simple diagnostic methods, the varied disease presentation, and the differentiation of

diabetic PN from other potential etiologies of PN.² Neuropathic symptoms usually begin with tingling or burning sensations, particularly in the calves, ankles, and feet, as well as a loss of vibratory sense. As neuropathic problems progress, the patient may lose all sensation in an area, resulting in the inability to detect heat, cold, or pain. Circulation to these areas also may be impaired secondary to atherosclerosis. The loss of neural function plus atherosclerosis may predispose the patient to infection and gangrene, especially in the toes, feet, and legs.⁴ This article reviews drug therapy to prevent, delay progression, and treat sensory PN.

Etiology and Pathogenesis

The exact etiology and pathogenesis of PN is unclear. PN may be the result of insulin deficiency or hyperglycemia coupled with poorly defined genetic or environmental factors.^{1,3} Several prominent theories have emerged to explain the pathogenesis of PN. These include (1) accumulation of sorbitol in the nerve cells, (2) decrease in nerve-free myoinositol and decreased activity of nerve sodium-potassium adenosine triphosphatase, (3) increased nonenzymatic peripheral nerve glycosylation, and (4) nerve hypoxia.

SORBITOL ACCUMULATION

Chronic hyperglycemia has been correlated with a decrease in nerve conduction velocity and the clinical symptoms of PN. Earlier studies linked sorbitol accumulation with late diabetic complications such as PN. Glucose usually is metabolized by hexokinase to glucose-6-phosphate. In the presence of persistent hyperglycemia, saturation of hexokinase occurs and excess glucose is converted to sorbitol by the polyol pathway. Animal studies have linked accumulation of sorbitol in the lenses of diabetic rats to the development of cataracts. Because sorbitol cannot diffuse easily out of the cell, the accumulation of sorbitol was thought to result in cellular toxicity and damage by a direct osmotic effect.⁵ This effect has been shown to explain the development of cataracts in persons with diabetes mellitus. However, it cannot be used to explain PN because the sorbitol concentration in nerve cells has been found to be too low to cause cellular toxicity or damage. Therefore, it is unlikely that the osmotic effects of increased sorbitol concentrations in the nerve and Schwann cells contribute to the pathogenesis of PN.

Piera T Calissi PharmD, Coordinator Clinical Services, Pharmacy Department, St Paul's Hospital (Grey Nuns), Saskatoon, Saskatchewan
Linda A Jaber PharmD, Assistant Professor, Pharmacy Practice, Wayne State University, 328 Shapiro Hall, 1400 Chrysler Service Dr, Detroit, MI 48202, FAX 313/577-5369
Reprints: Linda A Jaber PharmD

PERIPHERAL DIABETIC NEUROPATHY: CURRENT CONCEPTS IN TREATMENT

Piera T Calissi and Linda A Jaber

OBJECTIVE: To review pathophysiology and current concepts in the treatment of diabetic peripheral neuropathy (PN).

DATA SOURCES: References were identified through a MEDLINE search of the English-language literature from 1976 through 1994. Additional references were obtained from reference lists of articles identified through the search.

STUDY SELECTION AND DATA EXTRACTION: All articles were considered for possible inclusion in the review. Clinical trials that involved an adequate number of patients and review articles were selected. Information from articles that was judged by the authors to be significant was selected for discussion.

DATA SYNTHESIS: PN affects 5–50% of people with diabetes in the US and most commonly is characterized by tingling or burning sensations, particularly in the calves, ankles, and feet, with a loss of vibratory sense. Treatment of PN, for the most part, has been unsatisfactory. Therapy has been directed toward either improving nerve function or alleviating symptoms of PN, including pain and paresthesia. Glycemic control may slow the progression of PN. Hyperglycemia also is associated with decreased pain threshold in patients with diabetes mellitus. The aldose reductase inhibitors, particularly tolrestat, have been shown to improve objective and subjective neurologic function. Pain or paresthesia has been treated effectively with antidepressants, lidocaine, mexiletine, and capsaicin. The anticonvulsants phenytoin and carbamazepine may be effective, but are associated with a greater degree of adverse effects. Experimental treatments, such as gamma-linolenic acid, gangliosides, uridine, and the corticotropin_{4,9} analog ORG 2766, have been effective in improving neurologic function.

CONCLUSIONS: Treatment of PN remains unsatisfactory. Therapy should be directed toward prevention with glycemic control and symptomatic treatment of existing PN.

Ann Pharmacother 1995;29:769-77.

PERIPHERAL NEUROPATHY (PN) AFFECTS 5–50% of people with diabetes mellitus in the US.¹ The wide range in prevalence reflects the lack of agreement in a standard definition of PN.^{2,3} Factors contributing to a lack of a clear definition of PN include an absence of simple diagnostic methods, the varied disease presentation, and the differentiation of

diabetic PN from other potential etiologies of PN.² Neuropathic symptoms usually begin with tingling or burning sensations, particularly in the calves, ankles, and feet, as well as a loss of vibratory sense. As neuropathic problems progress, the patient may lose all sensation in an area, resulting in the inability to detect heat, cold, or pain. Circulation to these areas also may be impaired secondary to atherosclerosis. The loss of neural function plus atherosclerosis may predispose the patient to infection and gangrene, especially in the toes, feet, and legs.⁴ This article reviews drug therapy to prevent, delay progression, and treat sensory PN.

Etiology and Pathogenesis

The exact etiology and pathogenesis of PN is unclear. PN may be the result of insulin deficiency or hyperglycemia coupled with poorly defined genetic or environmental factors.^{1,3} Several prominent theories have emerged to explain the pathogenesis of PN. These include (1) accumulation of sorbitol in the nerve cells, (2) decrease in nerve-free myoinositol and decreased activity of nerve sodium-potassium adenosine triphosphatase, (3) increased nonenzymatic peripheral nerve glycosylation, and (4) nerve hypoxia.

SORBITOL ACCUMULATION

Chronic hyperglycemia has been correlated with a decrease in nerve conduction velocity and the clinical symptoms of PN. Earlier studies linked sorbitol accumulation with late diabetic complications such as PN. Glucose usually is metabolized by hexokinase to glucose-6-phosphate. In the presence of persistent hyperglycemia, saturation of hexokinase occurs and excess glucose is converted to sorbitol by the polyol pathway. Animal studies have linked accumulation of sorbitol in the lenses of diabetic rats to the development of cataracts. Because sorbitol cannot diffuse easily out of the cell, the accumulation of sorbitol was thought to result in cellular toxicity and damage by a direct osmotic effect.⁵ This effect has been shown to explain the development of cataracts in persons with diabetes mellitus. However, it cannot be used to explain PN because the sorbitol concentration in nerve cells has been found to be too low to cause cellular toxicity or damage. Therefore, it is unlikely that the osmotic effects of increased sorbitol concentrations in the nerve and Schwann cells contribute to the pathogenesis of PN.

Piera T Calissi PharmD, Coordinator Clinical Services, Pharmacy Department, St Paul's Hospital (Grey Nuns), Saskatoon, Saskatchewan

Linda A Jaber PharmD, Assistant Professor, Pharmacy Practice, Wayne State University, 328 Shapiro Hall, 1400 Chrysler Service Dr, Detroit, MI 48202, FAX 313/577-5369

Reprints: Linda A Jaber PharmD

MYOINOSITOL AND THE SODIUM-POTASSIUM ADENOSINE TRIPHOSPHATASE PUMP

Activation of the polyol pathway in the presence of hyperglycemia still may be important in the pathogenesis of PN. Activation of the polyol pathway has been implicated in a decrease of cellular myoinositol.^{1,5} Myoinositol is a precursor of polyphosphoinositol, an important component of plasma cell membranes and a required element for nerve cellular functions, including the transport of sodium, potassium, and calcium ions across cell membranes and nerve conduction. A sodium-dependent active transport system maintains the cellular concentration of myoinositol at a concentration 30–90 times that of plasma.

Insulin deficiency and hyperglycemia decrease the myoinositol concentration, resulting in a decreased nerve conduction velocity.⁵ This is thought to occur as a result of increased polyol pathway activity or inhibition of the sodium-dependent carrier-mediated myoinositol transport system. The role of myoinositol depletion is supported by the observation that normalization of myoinositol concentration by insulin administration, myoinositol supplementation, or treatment with aldose-reductase inhibitor restores decreased nerve conduction velocities in diabetic animals. Therefore, it is believed that polyol pathway overactivity is linked to myoinositol depletion. However, it is important to note that the same observation has not been seen consistently in humans with diabetes and PN. It is believed that the human subjects studied had already experienced structural damage to both microvessels and nerve fibers that was irreversible and, therefore, not reversible by these measures. The point at which early and reversible changes have progressed to irreversible changes has not been defined.

PROTEIN GLYCOSYLATION

Like the processes resulting in glycosylated hemoglobin, it has been hypothesized that hyperglycemia causes glycosylation of nerve myelin and a subsequent increase in myelin turnover and demyelination. In addition, glycosylation also may trap plasma proteins in myelin.¹ These changes to myelin are thought to result in neural damage or a decrease in nerve conduction.

NERVE HYPOXIA

In diabetic animals and humans, blood flow and oxygen tension are decreased. These changes may cause a decreased delivery of blood and oxygen to the nerves, which results in microvascular damage and further hypoxia.¹

Clinical Manifestations

Despite problems with recognition, diabetic PN has been subclassified into a number of clinical syndromes (Table 1).⁶ Sensory polyneuropathies are usually symmetrical, involve both sides of the body, and affect distal rather than proximal sensory nerves. When sensory polyneuropathy involves small fibers, pain and paresthesia in the legs and feet most commonly occur. The pain is described as dull, burning, lancinating, crushing, aching, or cramp-like. Paresthesia often is described as feelings of coldness, numbness, tingling, or burning. In addition, temperature and pain

perception may be decreased, especially in the legs and feet.¹

Positional and vibratory sensation impairment, manifest by diminished ankle reflexes and ataxia, are common features of large-fiber sensory neuropathy.⁶ Abnormalities of gait and Charcot joints sometimes are observed in the presence of proprioceptive fiber involvement with the possible complication of foot arch loss and multiple metatarsal bone fractures. Loss of stretch reflexes and vibratory sensation often are noted in physical examination. Overall, sensory polyneuropathies are the most common syndromes described and are usually more intense at night. Extremely painful periods often are limited to a few months or few years.⁶

Proximal motor neuropathies may present either in a symmetric or asymmetric pattern, and are subdivided clinically into acute, subacute, and chronically evolving. Acute and subacute, believed to be the result of neuromuscular junction ischemia, are usually manifested by the sudden onset of asymmetric weakness of the hip and thigh muscles with or without pain. Chronic motor neuropathies are thought to result from metabolic changes in the nerves. Symptoms usually resolve with restoration of glycemic control.

Cranial motor neuropathy, caused by occlusion of the vascular supply, is usually asymmetrical and involves mononeuropathy of cranial nerves III (oculomotor), IV (trochlear), and VI (abducens), the cranial nerves responsible for ocular movement, accommodation, and pupillary constriction, respectively. Neuropathy of these nerves results in extraocular muscle palsies (diabetic ophthalmoplegia).¹ The most common manifestation of diabetic ophthalmoplegia is diplopia that is preceded by severe retroorbital pain for 5–7 days in 50% of the cases. Onset of symptoms is sudden and dissipates when vascular supply is restored.

Mononeuropathies involving the median, ulnar, common peroneal, and femoral nerves, termed entrapment neuropathy of the limbs, are characterized by sudden wrist or foot drop. Truncal neuropathy (thoracoabdominal neuropathy) is usually self-limiting and is manifested by a gradual onset of burning pain in the lower anterior chest or upper abdomen. When several thoracic nerves are involved, weakness and denervation of the abdominal wall muscles may occur.

Alternately, the classification of PN has been described by Pfeifer et al. according to specific pain syndromes associated with the disease.⁷ These include superficial pain, deep pain, and muscular pain. Superficial pain, characterized by burning, allodynia, and tingling, is believed to be

Table 1. Classification of Diabetic Neuropathies⁶

Symmetric
distal, primarily sensory polyneuropathy
• mainly large fibers
• mixed
• mainly small fibers
chronically evolving proximal motor neuropathy
Asymmetric
acute or subacute proximal motor neuropathy
cranial motor neuropathy
truncal neuropathy
entrapment neuropathy of the limbs

caused by increased firing of damaged or abnormally excitable nociceptive fibers. Deep pain (e.g., pins and needles) is believed to be caused by spontaneous activity or increased sensitivity of damaged afferent fibers in the dorsal root ganglion and loss of inhibition of large myelinated and small unmyelinated fibers. Muscular pain (e.g., muscle cramping and spasm) is believed to be caused by damage to the reflex loop or to motor neurons.

Application of these systems and any other classification system of diabetic neuropathy is difficult in the clinical situation. Most patients do not fit well the clinical features of only 1 category and may have clinical features of several. A patient presenting with distal primary sensory polyneuropathy may have autonomic dysfunction, usually in the form of vasomotor dysfunction in the limbs and disturbances of sweating. Another difficulty is the lack of a relationship between the classification system and the pathogenesis of the specific neuropathic manifestation.

Diagnosis

Diagnostic assessment of diabetic PN is made on the basis of signs and symptoms plus a neurologic assessment of tendon reflex activity, touch, pressure, vibration, joint position, and pinprick perception. In clinical trials, quantitative assessment of vibratory and thermal sense plus conduction velocity measurement have been used to both diagnose and assess treatment response.^{5,8} Painful PN also can be assessed by using visual analog scales and validated questionnaires.

PN is difficult to diagnose because of a number of factors. First, there is an absence of a clear definition of diabetic neuropathy and PN has a varied presentation that may be outside currently described syndromes. Furthermore, the current methods for assessing the presence of PN are subjective, and the objective measures, such as conduction velocity and vibrational sense threshold, are not yet available for routine clinical application.

Prevention and Treatment

Treatment of PN, for the most part, has been unsatisfactory. Therapy has been directed toward either improving nerve function or alleviating symptoms of PN, including pain and paresthesia. A MEDLINE search covering the past 18 years (1976–1994) revealed almost 200 published articles dealing with the treatment of PN. For this review, only long-term, controlled clinical trials with an adequate number of patients were chosen.

PREVENTION BY GLYCEMIC CONTROL

A number of studies have evaluated the role of glycemic control on the progression of PN. Only recently has attainment of euglycemia with intensive insulin therapy been shown to delay the progression of PN. In a 2-year trial by the Steno Study Group,⁹ 33 patients with diabetes mellitus were randomized to receive either a standard regimen of 2 injections of intermediate-acting insulin daily or a continuous subcutaneous insulin infusion (CSII), designed to maintain normoglycemia. Glycemic control, as measured by glycosylated hemoglobin and mean blood glucose concentrations, were significantly lower in the group receiving the

CSII compared with those using the standard regimen. However, sensory nerve function, as measured by vibrational sense, was not significantly different.

In the Oslo study,¹⁰ 45 patients with diabetes mellitus were randomized to receive a standard regimen of 2 injections of regular and intermediate-acting insulin daily, multiple injections of regular insulin prior to each meal and at bedtime and intermediate-acting insulin at bedtime (i.e., 5–6 injections per day), or a CSII. Near normoglycemia was obtained in both the CSII and multiple-insulin injection groups, with slightly better control achieved with the CSII. Nerve function, as measured by motor conduction velocities in the tibial, peroneal, and ulnar nerves, deteriorated or was unchanged in the standard regimen and multiple-injection groups, but was improved significantly in the CSII group after 2 years of treatment.

In a study by Reichard et al.,¹¹ 102 patients were randomized to receive intensified treatment, consisting of intensive diabetic education and frequent follow-up or standard treatment, which provided routine but less intensive education and follow-up. Most of the patients in the intensive insulin group received 3 or more insulin injections daily. Patients were evaluated at 1.5, 3, 5, and 7.5 years. Glycemic control, as measured by glycosylated hemoglobin concentrations, was better in the intensive insulin therapy group. The number of patients with symptoms of PN increased in both groups, the difference not being significant. However, nerve function, as measured by conduction velocities of the ulnar, tibial, peroneal, and sural nerves deteriorated in both groups, but to the greatest extent in the standard treatment group.

Finally, in the Diabetes Control and Complications Trial (DCCT),¹² 1441 patients with insulin-dependent diabetes mellitus were randomized to receive either an intensified insulin regimen with 3 or more insulin injections daily and guided by frequent blood glucose monitoring or to conventional therapy, which consisted of 1 or 2 daily insulin injections for a mean follow-up period of 6.5 years. Patients were further divided into 2 cohorts, those with and those without preexisting retinopathy. Those with preexisting neuropathy at baseline were excluded. Glycemic control, as measured by glycosylated hemoglobin, was significantly better in those receiving intensive insulin therapy. In patients without retinopathy at baseline, intensive therapy reduced the development of clinical neuropathy (defined as an abnormal neurologic examination plus abnormal conduction velocity in at least 2 peripheral nerves or abnormal autonomic nerve testing) at 5 years by 69% (to 3% vs 10% in the conventional therapy group). In those patients with preexisting retinopathy, intensive insulin therapy reduced the appearance of clinical neuropathy at 5 years by 57% (to 7% vs 16% in the conventional therapy group).

It appears from these studies that patients who achieved near normal or normoglycemia with intensive insulin therapy had objective improvement in PN or decreased progression of PN.

Hyperglycemia may play a direct role in the development of symptoms. Hyperglycemia itself may be related to a decrease in the pain threshold. In 1 study,¹³ hyperglycemia induced by a glucose load decreased pain thresholds in diabetic patients, but not in normal volunteers. This suggests that increased glucose concentrations and/or rapid fluxes in glucose concentrations results in decreased pain tolerance.

In conclusion, glycemic control may prevent the development or progression of PN. Hyperglycemia also is associated with decreased pain threshold in patients with diabetes mellitus.

TREATMENT

Aldose Reductase Inhibitors. The aldose reductase inhibitors (e.g., sorbinil, ponalrestat, tolrestat) inhibit the conversion of glucose to sorbitol by the polyol pathway. This is believed to prevent a neuronal myoinositol deficiency, and increase the activity of the sodium-potassium adenosine triphosphatase pump, thereby preventing or slowing the neural structural damage and conduction velocity caused by overactivity of this pathway. Experience with these agents has been reviewed elsewhere.¹⁴ Studies with sorbinil and ponalrestat were stopped because of adverse effects and lack of efficacy. Studies with tolrestat have continued. Differences among the aldose reductase inhibitors may be expected because they are structurally dissimilar. In the first of these trials, Boulton et al.¹⁵ randomized 550 patients with diabetes and existing PN to receive tolrestat 200 mg/d or placebo for 12 months. At the end of the follow-up period, paresthesia symptom scores and motor conduction velocities improved significantly ($p < 0.05$) in the tolrestat group.

In a study by van Gerven et al.,¹⁶ 35 patients were randomized to receive tolrestat 200 mg/d or placebo for 6 months. This was followed by an open-label phase, during which all patients received tolrestat. After the first 6 months, motor conduction velocity, sensory and vibration perception thresholds worsened significantly in the group receiving placebo, but not in the treated group. Subjective improvement in neuropathic symptoms, as assessed by a 5-point scale, was not observed in either group. In the open-label phase of the trial, patients who initially received placebo demonstrated significant improvement in motor nerve conduction velocity and vibrational sensation after 6 months of treatment with tolrestat ($p < 0.05$). Those who received tolrestat in the initial 6-month double-blind phase showed improvement in either motor nerve conduction velocity or vibration sensation.

In a trial by Macleod et al.,¹⁷ 190 patients were randomized to receive tolrestat 200 mg/d or placebo for 6 months. Subjective assessment of paresthesia, but not pain, was significantly improved in those receiving tolrestat ($p < 0.02$). Motor nerve conduction velocity and vibration threshold significantly improved in some, but not all, sites tested ($p < 0.05$). Changes in sensory nerve conduction velocity were not significantly different between the groups. Three patients receiving tolrestat were withdrawn from the trial because of an increase in liver enzyme concentrations. Increases in alanine aminotransferase concentrations above baseline occurred in 34% of those treated with tolrestat and in 13% treated with placebo ($p < 0.005$).

In a trial by Guigliano et al.,¹⁸ 45 patients with mild autonomic and peripheral neuropathy were randomized to receive tolrestat 200 mg/d or placebo for 52 weeks. At the end of the study period, the vibrational threshold improved significantly in those treated with tolrestat, whereas vibrational threshold deteriorated in those receiving placebo ($p < 0.05$). Pain and paresthesia measured by a visual analog scale were present in 4 patients in the tolrestat group and in

3 in the placebo group. Three of the 4 patients in the tolrestat group improved, whereas the 3 in the placebo group experienced worsening symptoms. The small number of patients with significant neuropathic symptoms did not allow statistical analysis.

Finally, in a trial by Santiago et al.,¹⁹ 372 patients with PN who had received tolrestat for an average of 4.2 years were continued on tolrestat 200–400 mg/d or placebo for an additional 52 weeks. Pain scores worsened significantly ($p < 0.05$) in both groups compared with baseline. At 52 weeks, the mean pain score of tolrestat-treated patients was not significantly different from the placebo mean. The mean motor and sensory conduction velocities deteriorated significantly ($p < 0.05$) in those receiving placebo compared with baseline and with those receiving tolrestat.

Flaws in experimental design must be considered when interpreting the results. First, many of these trials were plagued by broad entry criteria and poorly defined endpoints. Therefore, it is difficult to know whether these agents would be beneficial in patients with specific pain syndromes or neuronal damage manifested by specific ranges in abnormal conduction velocity. Second, a commonly used endpoint, conduction velocity, measures the integrity of the large myelinated fibers, and therefore, conduction velocity improvements in smaller fibers would not be detected. Finally, animal data suggest that the longer PN is present, the less effective the aldose reductase inhibitors are. Therefore, the prophylactic use of these agents may need to be explored for safety and efficacy rather than for treatment of existing disease. Overall, however, the results of these trials appear to show some promise.

Antidepressants. Tricyclic antidepressants (TCAs) are used widely to treat painful PN. The TCAs are thought to relieve pain by blocking the central neuronal reuptake of serotonin and norepinephrine, thereby potentiating the inhibitory effect of these neurotransmitters on nociceptive pathways. Several clinical trials have evaluated the effectiveness of antidepressants in treating the painful symptoms of PN (Table 2).^{20–23} The effect of relieving pain appears to be independent of the antidepressant effect of these drugs.^{20,21} In randomized, double-blind, crossover trials, imipramine, amitriptyline, desipramine, clomipramine, and the combination of fluphenazine and nortriptyline have been found superior to placebo.^{20–27} Comparative trials suggest that the TCAs produce similar relief of symptoms.^{21,27} Some clinical trials showed a correlation between plasma concentrations and relief of neuropathic symptoms.^{20,21,28} For imipramine, achievement of target serum concentrations of 400–600 nmol/L (of imipramine plus desipramine) has been suggested to obtain maximal symptomatic relief.²⁸ The role of serum concentrations in clinical practice has not been established. However, serum concentrations may guide clinicians in dosage adjustments for patients receiving TCAs who still do not achieve symptomatic relief, as there appears to be a wide interpatient variation between dosage and serum concentration.

Two selective serotonin receptor reuptake inhibitors, paroxetine and citalopram, also appear to be effective in PN.^{29,30} In 1 study, both paroxetine and imipramine were found to be more effective than placebo.³⁰ In some patients paroxetine elicited a weaker therapeutic response than did imipramine. This may be attributed to the lower serum concentrations achieved with standard dosages. Optimal re-

sponse to paroxetine appeared to require serum concentrations in excess of 150–200 nM.

Fluoxetine, another selective serotonin receptor reuptake inhibitor, and the non-TCA mianserin have not been shown to work more effectively than placebo in clinical trials.^{27,31} Fluoxetine effectiveness was not correlated with serum concentrations achieved with 20–40 mg/d. Dosages of fluoxetine of more than 40 mg have not been studied.

Capsaicin. In addition to the antidepressants, capsaicin has been shown to be effective in relieving pain associated with PN.^{32–34} Capsaicin appears to alleviate pain and burning by stimulating the release and subsequent depletion of substance P from sensory fibers. It also may block substance P axonal transport. Vibration, temperature, and touch perception are not altered.³⁴

In a trial by the Capsaicin Study Group,^{32,33} 277 patients were randomized to apply capsaicin 0.075% cream or vehicle 4 times daily for 8 weeks. Pain assessment and relief, as measured by a physician's global evaluation (PGE) and by visual analog scale, showed capsaicin to be significantly ($p < 0.05$) more effective than placebo. A substantial

placebo effect with the vehicle was observed. In a trial by Tandan et al., patients were randomized to apply capsaicin 0.075% cream or vehicle 4 times daily for 8 weeks. Pain assessment and relief as measured by a PGE showed capsaicin to be more effective than the vehicle. However, pain intensity, as assessed by the visual analog scale, was not significantly different between the groups.³⁴

The results of these trials were not confirmed by Chad et al.,³⁵ who randomized 58 patients with painful PN to apply capsaicin 0.075% cream or vehicle 4 times daily for 4 weeks. Pain assessment and relief as measured by PGE, visual analog scale, and a categorical pain scale were not significantly different between groups.

Finally, Zhang and Li-Wan-Po³⁶ evaluated the effectiveness of topical capsaicin in diabetic neuropathy, using a meta-analysis of clinical trials. They found that capsaicin cream resulted in more pain relief than placebo, with an odds ratio of 2.74 (95% confidence interval 2.77 to 6.88) in favor of capsaicin.

Capsaicin therapy may have a number of inherent problems, which include poor compliance associated with fre-

Table 2. Summary of Trials with Antidepressants in Diabetic Patients with Peripheral Neuropathy

REF.	DESIGN	TREATMENT	OUTCOME/EFFECT
Max et al. (1987) ²⁰	29 patients with painful PN; assessment of pain by patient diary and global assessment, depression by HDS	amitriptyline 25–150 mg/d or placebo ^b × 6 wk, then crossed over × 6 wk	amitriptyline improved global assessment scores ($p < 0.0001$); this effect was not influenced by the presence or absence of depression
Sindrup et al. (1990) ²¹	26 patients with painful PN; assessment by Neuropathic 6-Item Observer Scale ^a	clomipramine 50–75 mg/d, desipramine 50–200 mg/d, or placebo × 2 wk, then crossed over	clomipramine and desipramine decreased neuropathic symptoms ($p < 0.05$); clomipramine tended to be more efficacious than desipramine
Sindrup et al. (1989) ²²	9 patients with painful PN; assessment by Neuropathic 6-Item Observer Scale ^a	imipramine 50–75 mg ^c or placebo × 3 weeks, then crossed over × 3 wk	imipramine decreased neuropathic symptoms over placebo ($p < 0.01$)
Max et al. (1991) ²³	20 patients with painful PN; pain assessment by patient diary and global assessment	desipramine 12.5–150 mg/d or placebo ^b × 6 wk, then crossed over	desipramine decreased painful symptoms compared with placebo ($p < 0.01$); pain relief tended to be greater in depressed patients
Kvinesdal et al. (1984) ²⁴	12 patients with severe painful PN; assessment by Neuropathic 6-Item Observer Scale ^a and global assessment	imipramine 100 mg/d or placebo × 5 wk, then crossed over × 5 wk	imipramine caused improvement in global assessment scores compared with placebo ($p < 0.02$), but not neuropathic score ($p < 0.1$)
Gomez-Perez et al. (1985) ²⁵	18 patients with painful PN; assessment of pain and paresthesia by visual analog scale	nortriptyline 60 mg + fluphenazine 3 mg combination or placebo daily × 30 d, then crossed over for 30 d	nortriptyline–fluphenazine decreased pain and paresthesia scores compared with placebo ($p < 0.01$)
Max et al. (1992) ²⁷	57 patients with painful PN; pain assessment by patient diary and global assessment, depression by HDS	desipramine 12.5–150 mg/d, amitriptyline 12.5–150 mg/d, fluoxetine 20–40 mg/d or placebo ^b × 6 wk, then crossed over	desipramine and amitriptyline decreased painful symptoms compared with baseline; fluoxetine was no more effective than placebo in relieving painful symptoms; no correlation between effect and serum concentration of drugs observed
Sindrup et al. (1992) ²⁹	15 patients with painful PN; assessment by Neuropathic 6-Item Observer Scale ^a	citalopram 40 mg/d or placebo × 3 wk, then crossed over	citalopram decreased neuropathic symptoms compared with placebo ($p < 0.02$); no correlation between serum concentration and effect
Sindrup et al. (1990) ³⁰	29 patients with painful PN; assessment by Neuropathic 6-Item Observer Scale ^a	imipramine 50–75 mg/d, ^c paroxetine 40 mg/d or placebo × 2 wk, then crossed over	imipramine and paroxetine decreased neuropathic symptoms ($p < 0.02$), with imipramine showing a greater effect than paroxetine
Sindrup et al. (1992) ³¹	18 patients with painful PN; assessment by Neuropathic 6-Item Observer Scale ^a	imipramine 25–350 mg/d, ^c mianserin 60 mg/d, or placebo × 2 wk, then crossed over	imipramine decreased neuropathic symptoms compared with placebo and mianserin ($p = 0.030$ and $p = 0.033$, respectively); mianserin resulted in no improvement in neuropathic symptoms when compared with imipramine or placebo

HDS = 21-item Hamilton Depression Scale; PN = peripheral neuropathy.

^aNeuropathic 6-Item Observer Scale domains include pain, dysesthesia, paresthesia, numbness, nocturnal deterioration, and sleep disturbances.

^bPlacebo = benzotropine 0.5–1 mg used to mimic dry mouth of the tricyclic antidepressants.

^cImipramine dosage titrated to obtain serum concentration of 400–600 nmol/L achieved with imipramine plus desipramine.

quent application and with adverse effects, such as burning, redness, and stinging at the application site. Neurotoxicity resulting in functional impairment of sensory fibers has been observed in experimental trials and may limit long-term use.^{37,38}

Lidocaine and Mexiletine. Lidocaine and mexiletine are class I-B antiarrhythmic agents. In a study by Kastrup et al.,³⁹ 15 patients with diabetes mellitus and painful PN received a 30-minute infusion of lidocaine 5 mg/kg or a placebo (NaCl 0.9%) in a double-blind, crossover fashion. Lidocaine was shown to decrease painful symptoms of PN significantly ($p < 0.05$) for a duration ranging from 3 to 21 days. Similarly, in a trial by Dejgaard et al.,⁴⁰ 16 diabetic patients with painful PN were randomized to receive mexiletine 10 mg/kg/d po for 26 weeks in a double-blind, placebo-controlled, crossover trial. Pain, as assessed by subjective scoring, was decreased significantly in the mexiletine, but not the placebo-treated, group. Finally, in a trial by Stracke et al.,⁴¹ 95 diabetic patients were randomized to receive mexiletine 225 mg po tid or matched placebo for 5 weeks. Mexiletine appeared to be effective in diabetic patients with PN who had burning or stabbing pain, heat sensations, and formication-type discomfort. These studies suggest that both lidocaine and mexiletine are useful to decrease symptoms in patients with diabetes mellitus who experience painful PN.

Phenytoin and Carbamazepine. Both phenytoin and carbamazepine appear to be effective in the treatment of pain associated with PN. In an early study by Ellenburg,⁴² 60 patients with diabetes mellitus who had symptomatic neuropathy received phenytoin 100 mg po 3 to 4 times daily. Serum phenytoin concentrations were not monitored. Of these patients, 51 reported symptomatic improvement in symptoms, primarily pain and paresthesia. The results of this study, however, were not confirmed by Saudek et al.,⁴³ whose 12 patients received phenytoin or placebo in a double-blind, crossover fashion. Dosages were adjusted to achieve serum concentrations between 5 and 20 mg/L. In addition to observing no effect on pain or paresthesia, the investigators observed that patients receiving phenytoin had increased blood sugar concentrations and a high degree of adverse effects such as ataxia, blurred vision, dizziness, and rash. No correlation between serum concentrations and efficacy was observed.

In a study by Rull et al.,⁴⁴ a total daily dosage of carbamazepine 600 mg was compared with placebo in a crossover, double-blind trial. Serum concentrations were not monitored. In the 30 patients with diabetes mellitus studied, 28 reported symptomatic relief of pain and paresthesia while receiving carbamazepine. Adverse effects included somnolence, dizziness, gait changes, urticaria, nausea, and vomiting. Most of the adverse effects reported were mild and transient. The development of urticaria required discontinuation of the drug.

Because of the high degree of adverse effects, the use of anticonvulsants for treatment of pain and paresthesia should be limited to patients in whom other treatments have failed. Carbamazepine may be the preferred agent, as it is not associated with increases in blood glucose concentration and has fewer intolerable adverse effects.

Comprehensive Management. Pfeifer et al.⁷ have explored a comprehensive approach in the management of painful PN. In a controlled case study, 75 patients with dia-

betes mellitus and painful PN received 1 of 3 treatment protocols or no treatment. Pain in the treated group was categorized and treated as follows: Those with superficial pain were treated with capsaicin 0.075% cream applied 4 times daily. Deep pain was treated with imipramine 50–150 mg po hs. If imipramine therapy was not effective or tolerated, mexiletine was added or substituted and titrated to a maximum dosage of 10 mg/kg/d in divided doses. Muscular pain was treated with stretching exercises and the muscle relaxant metaxolone 800 mg po 3 to 4 times daily. Piroxicam therapy was added if metaxolone and the stretching exercises were not effective. All treatments were continued for 3 months. Pain, as assessed by a graphic rating scale, was decreased significantly ($p = 0.001$) in the treatment group compared with the untreated group. Capsaicin was well-tolerated and imipramine provided excellent pain relief, so that addition of mexiletine was largely unnecessary. Those who received mexiletine could not tolerate imipramine secondary to urinary retention or postural hypotension. Metaxolone also was well-tolerated, with 3 patients requiring dosage reduction because of nausea or sedation. This comprehensive approach to management of painful PN in patients with diabetes mellitus is a further refinement of the single drug treatments used in the previously discussed studies. However, further double-blind, controlled studies are required to confirm these results. Important is the addition of a placebo arm to such studies, as the placebo effect of these treatments, especially capsaicin, may be substantial.

EXPERIMENTAL TREATMENTS

Gamma-Linolenic Acid. Gamma-linolenic acid is an essential component of myelin and the neuronal cell membrane. The synthesis of gamma-linolenic acid from linoleic acid is disturbed in patients with diabetes mellitus, the degree of which is correlated to glycosylated hemoglobin concentrations. Therefore, it is believed that a decrease in the concentration of gamma-linolenic acid is associated with development of PN.

In 2 trials, the effect of gamma-linolenic acid was studied in patients with PN. In the first of these trials, patients received gamma-linolenic acid (from evening primrose oil) 360 mg/d for 6 months.⁴⁵ In the second trial, patients were given 480 mg/d for 12 months. In both studies subjective plus objective improvements in conduction velocity, heat and sensation indices, tendon reflexes, and muscle strength were noted.⁴⁶ Both studies indicated that gamma-linolenic acid may have a beneficial role in the treatment of PN.

Gangliosides. Gangliosides are complex sialoglycolipids found in nerve tissue, which appear in animal studies to promote regeneration of synapses.⁴⁷ In clinical trials, mixed bovine gangliosides have been shown to improve the activity of neural sodium–potassium adenosine triphosphatase and to restore impaired electrophysiologic parameters in diabetic rats. Several double-blind, placebo-controlled trials have evaluated the effect of gangliosides in dosages of 20–40 mg/d im given for 6–16 weeks to patients with diabetes mellitus with PN. In some, but not all, of the studies modest improvements in sensory and motor conduction velocity as well as subjective improvement in symptoms have been found.^{47–52} Additional long-term stud-

ies are required to evaluate the role of gangliosides in the treatment of PN.

Uridine. Uridine, a pyrimidine base and precursor to RNA, is believed to increase the synthesis of cytosine triphosphate. Cytosine triphosphate promotes the synthesis of phosphatidylinositol, which is required for the functioning of the sodium-potassium adenosine triphosphatase pump in neural cells and is thought to be deficient in patients with PN. Uridine monophosphate, which is derived from uridine, promotes the biotransformation of glucose 1-phosphate to glycogen. Transformation of excess glucose into glycogen may discourage activation of the polyol pathway and protein glycosylation. Furthermore, uridine may promote synthesis of polyphosphinositol, a component of plasma membranes and a required element of nerve cellular functions.⁵³

In a 6-month, double-blind, placebo-controlled trial involving 40 diabetic patients with PN,⁵³ uridine 300 mg/d tid improved conduction velocity in all nerves tested. The authors concluded that uridine may be effective in the treatment of PN.

Corticotropin_{4,9} Analog. The corticotropin_{4,9} analog ORG 2766 is a neuropeptide that exhibits a neurotropic effect on damaged peripheral nervous tissue, accelerating tissue repair.⁵⁴ In a double-blind, placebo-controlled trial involving 62 patients with diabetic neuropathy,⁵⁴ the corticotropin_{4,9} analog, ORG 2766, 3 mg/d sc for 1 year significantly ($p < 0.05$) improved vibration threshold. However, other parameters, including conduction velocity, remained unchanged. The authors concluded that ORG 2766 may be effective in improving the vibration threshold, indicating large myelinated fiber function, but not other neural physiologic function tests.

Other Agents. Pentoxifylline and cyclandelate are rheologic agents that improve erythrocyte deformability, thereby improving blood flow through partially occluded vessels. Because microvascular diseases may contribute to diabetic neuropathy by depriving nerve cells of blood and oxygen, an agent that improves blood flow should theoretically delay or retard progression of PN. However, in 2 separate studies,^{55,56} both pentoxifylline and cyclandelate were found to be no more effective than placebo in the treatment of PN.

Clonidine has been shown to be effective in the treatment of a number of painful disorders, including postoperative pain, cancer pain, pain associated with arachnoiditis, and postherpetic pain. However, in a trial of patients with pain associated with PN, clonidine was no more effective than placebo.⁵⁷

Summary

PN is a significant complication of diabetes mellitus. Drug therapy has been only partially successful in preventing or reversing the progression or alleviating the symptoms of PN.

Normalization of blood glucose concentrations may prevent the development or progression of PN. In addition, the aldose reductase inhibitors need to be studied to determine if they have a role in the prevention or progression of PN. Likewise, glycemic control and the aldose reductase inhibitors may be effective in the treatment of PN. Other treatments such as gamma-linolenic acid, gangliosides,

and uridine require further study to determine their role in the treatment of PN.

Pain associated with PN may be treated successfully with antidepressants, such as TCAs, and the SSRIs paroxetine, mexiletine, and capsaicin. Selection of the best agent may depend on the specific pain syndrome or severity of symptoms that the patient exhibits. The anticonvulsants phenytoin and carbamazepine should be considered third-line agents, as their use is associated with a high degree of possible adverse reactions. ≈

References

- Harati Y. Review. Diabetic peripheral neuropathies. *Ann Intern Med* 1987; 107:546-59.
- Maser RE, Nielsen VK, Bass E, Manjou Q, Dorman JG, Kelsey SF, et al. Measuring diabetic neuropathy. Assessment and comparison of clinical examination and quantitative sensory testing. *Diabetes Care* 1989;12: 270-5.
- Martin RA. Management of peripheral neuropathy in diabetes mellitus. Recent research findings and their therapeutic implication. *Postgrad Med* 1987;82:183-7.
- Francisco GE, Brooks PJ. Diabetes mellitus. In: Dipiro JT, Talbert RL, Haynes PE, Yee GC, Matzke GR, Posey LM, et al. ed. *Pharmacotherapy. A pathophysiologic approach*. 2nd ed. New York: Elsevier Science, 1992:1121-45.
- Masson EA, Boulton AJM. Aldose reductase inhibitors in the treatment of diabetic neuropathy. A review of the rationale and clinical evidence. *Drugs* 1990;39:190-202.
- Ashbarg AK. Diseases of the peripheral nervous system. In: Wilson JD, Braunwald E, Isselbacher KJ, Petersdorf RG, Martin JB, Fauci AS, et al. ed. *Harrison's principles of internal medicine*. 12th ed. New York: McGraw-Hill, 1991:2096-107.
- Pfeifer MA, Ross DR, Schrage JP, Gelber DA, Schumer MP, Crain GM, et al. A highly successful and novel model for treatment of chronic painful diabetic peripheral neuropathy. *Diabetes Care* 1993;16:1102-15.
- American Diabetes Association. Diabetic neuropathy (consensus statement). *Diabetes Care* 1993;16:66-71.
- Lauritzen T, Frost-Larsen K, Larsen HW, Deckert T. Two-year experience with continuous subcutaneous insulin infusion in relation to retinopathy and neuropathy. *Diabetes* 1985;34(suppl 3):74-9.
- Dahl-Jørgensen K, Brinchmann-Hansen O, Hanssen KF, Ganes T, Kierulf P, Smeland E, et al. Effect of near normoglycaemia for two years on progression of early diabetic retinopathy, nephropathy, and neuropathy: the Oslo study. *Br Med J* 1986;293:1195-9.
- Reichard P, Bengt-Yngve N, Rosenqvist U. The effect of long-term intensified insulin treatment on the development of microvascular complications of diabetes mellitus. *N Engl J Med* 1993;329:304-9.
- The Diabetes Control and Complications Trial Research Group, ed. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329:977-86.
- Morley GK, Mooradian AD, Levine AS, Morley JE. Mechanism of pain in diabetic peripheral neuropathy. Effect of glucose on pain perception in humans. *Am J Med* 1984;77:79-82.
- Tsai SC, Burnakis TG. Aldose reductase inhibitors: an update. *Ann Pharmacother* 1993;27:751-4.
- Boulton AJM, Levin S, Comstock J. Multicentre trial of the aldose-reductase inhibitor, tolrestat, in patients with symptomatic diabetic neuropathy. *Diabetologia* 1990;33:431-7.
- van Gerven J, Lemkes H, van Kijk J. Long-term effects of tolrestat in symptomatic diabetic sensory polyneuropathy. *J Diabetes Complications* 1992;6:45-8.
- Macleod AF, Boulton AJM, Owens DR, van Rooy P, van Gerven JMA, Macrury S, et al. A multicentre trial of the aldose reductase inhibitor tolrestat, in patients with symptomatic diabetic peripheral neuropathy. *Diabetologia* 1992;18:14-20.
- Guigliano D, Marfella R, Quatraro A, De Rosa N, Salvatore T, Cozzolino D, et al. Tolrestat for mild diabetic neuropathy. A 52-week, randomized, placebo-controlled trial. *Ann Intern Med* 1993;118:7-11.
- Santiago JV, Sönksen PH, Boulton AJM, Macleod A, Beg M, Bockenek W, et al. Withdrawal of the aldose reductase inhibitor tolrestat in pa-

- tients with diabetic neuropathy: effect on nerve function. *J Diabetes Complications* 1993;7:170-8.
20. Max MB, Culnane M, Schafer SC, Gracely RH, Walther DJ, Smoller B, et al. Amitriptyline relieves diabetic neuropathy pain in patients with normal or depressed mood. *Neurology* 1987;37:589-96.
 21. Sindrup SH, Gram LF, Skjold T, Grodum E, Brøsen K, Beck-Nielsen H. Clomipramine vs desipramine vs placebo in the treatment of diabetic neuropathy symptoms. A double-blind cross-over study. *Br J Clin Pharmacol* 1990;30:683-91.
 22. Sindrup SH, Ejlersen B, Frøland A, Sindrup EH, Brøsen K, Gram LF. Imipramine treatment in diabetic neuropathy: relief of subjective symptoms without changes in peripheral and autonomic nerve function. *Eur J Clin Pharmacol* 1989;37:151-3.
 23. Max MB, Kishore-Kumar R, Schafer SC, Meister B, Gracely RH, Smoller B, et al. Efficacy of desipramine in painful diabetic neuropathy: a placebo-controlled trial. *Pain* 1991;45:3-9.
 24. Kvinesdal B, Molin J, Frøland A, Gram LF. Imipramine treatment of painful diabetic neuropathy. *JAMA* 1984;251:1727-30.
 25. Gomez-Perez FJ, Rull JA, Dies H, Rodriguez-Rivera JG, Gonzalez-Barraño J, Lozano-Castañeda O. Nortriptyline and fluphenazine in the symptomatic treatment of diabetic neuropathy. A double-blind cross-over study. *Pain* 1985;23:395-400.
 26. Watson CPN. Comment on the paper by Mitchell B. Max et al. on 'Efficacy of desipramine in painful diabetic neuropathy: a placebo-controlled trial.' *Pain* 1991;45:1-2.
 27. Max MB, Lynch SA, Muir J, Shoaf SE, Smoller B, Dubner R. Effects of desipramine, amitriptyline and fluoxetine on pain in diabetic neuropathy. *N Engl J Med* 1992;326:1250-6.
 28. Sindrup SH, Gram LF, Skjold T, Frøland A, Beck-Nielsen H. Concentration-response relationship in imipramine treatment of diabetic neuropathy symptoms. *Clin Pharmacol Ther* 1990;47:509-15.
 29. Sindrup SH, Bjerre U, Dejgaard A, Brøsen K, Aaes-Jørgensen T, Gram LF. The selective serotonin reuptake inhibitor citalopram relieves the symptoms of diabetic neuropathy. *Clin Pharmacol Ther* 1992;52:547-52.
 30. Sindrup SH, Gram LF, Brøsen K, Eshøj, Morgensen EF. The selective serotonin reuptake inhibitor paroxetine is effective in the treatment of diabetic neuropathy symptoms. *Pain* 1990;42:135-44.
 31. Sindrup SH, Tuxen C, Gram LF, Grodum E, Skjold T, Brøsen K, et al. The effect of mianserin on the symptoms of diabetic neuropathy. *Eur J Clin Pharmacol* 1992;43:251-5.
 32. The Capsaicin Study Group. The effect of treatment with capsaicin on daily activities of patients with painful diabetic neuropathy. *Diabetes Care* 1992;15:159-66.
 33. The Capsaicin Study Group. Treatment of diabetic neuropathy with topical capsaicin. A multicenter, double-blind, vehicle-controlled study. *Arch Intern Med* 1991;151:2225-9.
 34. Tandan R, Lewis GA, Krusinski PB, Badger GB, Fries TJ. Topical capsaicin in painful diabetic neuropathy. *Diabetes Care* 1992;15:8-14.
 35. Chad DA, Aronin N, Lundstrom R, McKeon P, Ross D, Molitch M, et al. Does capsaicin relieve the pain of diabetic neuropathy? *Pain* 1990;42:387-8.
 36. Zhang WY, Li-Wan-Po A. The effectiveness of topically applied capsaicin. A meta-analysis. *Eur J Clin Pharmacol* 1994;46:517-22.
 37. Levy DM, Abraham RR. Topical capsaicin in the treatment of painful diabetic neuropathy. *N Engl J Med* 1991;324:776-7.
 38. Rumsfield JA, West DP. Topical capsaicin in dermatologic and peripheral pain disorders. *DICP Ann Pharmacother* 1991;25:381-7.
 39. Kastrup J, Petersen P, Dejgård A, Angelo HR, Hilsted J. Intravenous lidocaine infusion—a new treatment of chronic painful diabetic neuropathy? *Pain* 1987;28:69-75.
 40. Dejgård A, Petersen P, Kastrup J. Mexiletine for treatment of chronic painful diabetic neuropathy. *Lancet* 1988;1:9-11.
 41. Stracke H, Meyer UE, Schumacher HE, Federlin K. Mexiletine in the treatment of diabetic neuropathy. *Diabetes Care* 1992;15:1550-5.
 42. Ellenberg M. Treatment of diabetic neuropathy with diphenylhydantoin. *N Y State J Med* 1968;68:2653-5.
 43. Saudek CD, Werns S, Reidenberg MM. Phenytoin in the treatment of diabetic symmetrical polyneuropathy. *Clin Pharmacol Ther* 1977;22:196-9.
 44. Rull JA, Quibrera R, González-Millán H, Castañeda OL. Symptomatic treatment of peripheral diabetic neuropathy with carbamazepine (Tegretol): double blind crossover trial. *Diabetologia* 1989;5:215-8.
 45. Jamal GA, Carmichael H. The effect of γ -linolenic acid on human diabetic peripheral neuropathy: a double-blind placebo-controlled trial. *Diabetic Med* 1990;7:319-23.
 46. The γ -Linolenic Acid Multicenter Trial Group. Treatment of diabetic neuropathy with gamma-linolenic acid. *Diabetes Care* 1993;16:8-14.
 47. Abraham RR, Abraham RM, Wynn V. A double blind placebo controlled trial of mixed gangliosides in diabetic peripheral neuropathy. In: Ledeer RW, Yu RK, Rapport MM, Suzuki K, eds. Ganglioside structure, function and biomedical potential. Advances in experimental medicine and biology. Vol. 174. New York: Plenum Press, 1984:607-24.
 48. Horowitz SH. Ganglioside (cronicassial) therapy in diabetic neuropathy. In: Ledeer RW, Yu RK, Rapport MM, Suzuki K, eds. Ganglioside structure, function and biomedical potential. Advances in experimental medicine and biology. Vol. 174. New York: Plenum Press, 1984:593-600.
 49. Liniger C, Pernet A, Moody JF, Assal J-P. Effect of gangliosides on diabetic peripheral neuropathy. *Diabetes Res Clin Pract* 1989;7:251-8.
 50. Naarden A, Davidson J, Harris L, Moore J, DeFelicis S. Treatment of painful diabetic polyneuropathy with mixed gangliosides. In: Ledeer RW, Yu RK, Rapport MM, Suzuki K, eds. Ganglioside structure, function and biomedical potential. Advances in experimental medicine and biology. Vol. 174. New York: Plenum Press, 1984:581-92.
 51. Fedele D, Crepaldi G, Leontino B. Multicentre trial on gangliosides in diabetic peripheral neuropathy. In: Ledeer RW, Yu RK, Rapport MM, Suzuki K, eds. Ganglioside structure, function and biomedical potential. Advances in experimental medicine and biology. Vol. 174. New York: Plenum Press, 1984:601-6.
 52. Hallett M, Flood T, Slater N, Dambrosia J. Trial of ganglioside therapy for diabetic neuropathy. *Muscle Nerve* 1987;10:822-5.
 53. Gallai V, Mazzotta G, Montesi S, Sarchielli P, Del Gatto F. Effects of uridine in the treatment of diabetic neuropathy: an electrophysiological study. *Acta Neurol Scand* 1992;86:3-7.
 54. Bravenboer B, Hendrikse PH, Oey PL, van Huffelen AC, Groenhouut C, Gispen WH, et al. Randomized double-blind placebo-controlled trial to evaluate the effect of the ACTH_{4,9} analogue, ORG 2766, in IDDM patients with neuropathy. *Diabetologia* 1994;37:408-13.
 55. Heimans JJ, Drukarch B, Matthaei I, Ijft GA, Bertelsmann FW, Strijers RLM, et al. Cyclandelate in diabetic neuropathy. A double-blind, placebo-controlled, randomized, cross-over study. *Acta Neurol Scand* 1991;84:483-6.
 56. Cohen KL, Lucibello FE, Chomiak M. Lack of effect of clonidine and pentoxifylline in short-term therapy of diabetic peripheral neuropathy. *Diabetes Care* 1990;13:1074-7.
 57. Zeigler D, Lynch SA, Muir J, Benjamin J, Max MB. Transdermal clonidine versus placebo in painful diabetic neuropathy. *Pain* 1992;48:402-8.

EXTRACTO

OBJETIVO: Discutir la patofisiología y conceptos actualizados sobre el tratamiento de la neuropatía periférica (NP) diabética.

FUENTES DE INFORMACIÓN: Búsqueda bibliográfica en MEDLINE de artículos en inglés publicados durante el período de 1976-1994. Las listas de referencias de estos artículos fueron revisadas para identificar otros artículos de interés.

SELECCIÓN DE FUENTES DE INFORMACIÓN Y MÉTODO DE EXTRACCIÓN: Se consideraron todos los artículos identificados en la búsqueda bibliográfica. Se seleccionaron artículos que discutían estudios clínicos en donde se incluyó un número adecuado de pacientes y artículos donde se revisó la literatura. De estos artículos, los autores seleccionaron la información necesaria para generar su discusión.

SÍNTESIS: La NP afecta aproximadamente 5-50% de los diabéticos en los Estados Unidos. Esta se caracteriza por una sensación de cosquilleo o quemazón, primordialmente en las pantorillas, los tobillos, y los pies, acompañada de una pérdida de sentido de vibración. El tratamiento para la NP ha sido, generalmente, poco satisfactorio. La terapia ha sido dirigida a mejorar la función nerviosa o aliviar los síntomas de NP incluyendo el dolor y la parestesia. El control glicémico puede detener la progresión de la NP. La hiperglicemia ha sido asociada con una tolerancia más baja de dolor en pacientes con diabetes mellitus. Se ha demostrado que los inhibidores de la aldosa reductasa, en particular tolrestat, mejoran la función neurológica objetiva y subjetiva. El dolor y la parestesia han sido tratados con efectividad con antidepresivos, lidocaína, mexiletina, y capsaicina. La fenitoina y la carbamazepina pueden ser efectivos en el tratamiento del dolor y la parestesia, pero éstos agentes están asociados con un mayor número de efectos secundarios. Existen tratamientos con agentes experimentales, tales

como el ácido gamalinoleico, los gangliósidos, la uridina, y el análogo de ACTH_{4,9} denominado ORG 2766, los cuales han demostrado ser efectivos en mejorar la función neurológica.

CONCLUSIONES: El tratamiento de NP continua siendo poco satisfactorio. La terapia debe estar dirigida hacia la prevención de la condición por medio del control glicémico y el tratamiento de síntomas asociados a NP en pacientes que padecen de la condición.

HOMERO A MONSANTO

RÉSUMÉ

OBJECTIF: Réviser la pathophysiologie et les concepts courants du traitement de la neuropathie périphérique diabétique.

REVUE DE LITTÉRATURE: Les références de langue anglaise ont été identifiées à l'aide d'une recherche sur MEDLINE pour la période de 1976–1994. Des références supplémentaires ont été identifiées à l'aide de la liste des références des articles identifiés par la recherche.

SÉLECTIONS DES ÉTUDES ET DE L'INFORMATION: Tous les articles identifiés par la recherche ont été retenus. Les études cliniques qui avaient inclus un nombre suffisant de sujets ainsi que les articles de revue ont été sélectionnés. Les auteurs ont jugé de la pertinence de l'information à inclure dans cette revue.

RÉSUMÉ: La neuropathie périphérique affecte de 5–50% des diabétiques aux États-Unis. Elle se manifeste par des fourmillements et des brûlures aux mollets, aux chevilles, et aux pieds associés à une perte de la

sensation de vibration. À ce jour, le traitement de la neuropathie périphérique s'est avéré insatisfaisant. La thérapie actuelle cible l'amélioration de la fonction neurologique ou le soulagement de la douleur et des paresthésies. Le contrôle de la glycémie ralentirait la progression de la neuropathie périphérique. L'hyperglycémie est associée avec une diminution du seuil de la douleur chez les diabétiques. Les inhibiteurs de l'aldose réductase, notamment le tolrestat, ont démontré une amélioration subjective et objective de la fonction neurologique. La douleur ou les paresthésies peuvent être traitées efficacement avec les antidépresseurs, la lidocaïne, la mexilétine, et la capsaïcine. La phénytoïne et la carbamazépine peuvent être efficaces, mais sont associées à une incidence plus élevée d'effets indésirables. Des thérapies expérimentales telles l'acide gamma-linolénique, les gangliosides, l'uridine, et l'analogue de l'ACTH_{4,9}, ORG 2766, se sont avérées efficaces dans l'amélioration de la fonction neurologique.

CONCLUSIONS: Le traitement actuel de la neuropathie diabétique est peu satisfaisant. La thérapie doit cibler la prévention par un contrôle de la glycémie ou s'orienter vers le traitement symptomatique.

MONIQUE RICHER