

Transdermal Gels *in the* Treatment of Diabetic Neuropathy

They offer pain relief with a reduced risk of side effects.

Recent data have estimated the prevalence of diabetic neuropathy as ranging from 10% to 90% of the entire diabetic population. *Diabetic neuropathy* refers to a large number of clinical syndromes that affect both the autonomic and peripheral nervous system¹ and affect both type 1 and type 2 diabetes patients. It presents as a loss of sensation in the extremities of the body due to nerve-fiber damage that leads to a decrease in the quality of life for patients.² There are several common forms of diabetic neuropathy but the most prevalent is distal symmetrical sensorimotor polyneuropathy.³ With this type of neuropathy, patients mostly complain of paresthesias of the feet. Although diagnosis of this disease is generally straightforward, treatment can prove to be a difficult task.⁴ Particular emphasis will be placed on the use of ketamine Pluronic® lecithin organogels (PLOs) for the treatment of diabetic neuropathy.

Etiology

Although there are several theories on the etiology of diabetic neuropathy, its cause is not well defined. Its varying pathology suggests that there are various pathological mechanisms by which nerve damage is occurring. One theory proposes that persistent hyperglycemia causes sorbitol and fructose to accumulate in the nerve cells due to amplification of the greater polyol pathway. This increased concentration of sorbitol and fructose causes damage to nerve fibers by an unknown mechanism. This is accompanied by inhibition of the Na⁺/K⁺ ATPase, resulting in sodium retention, edema and nerve degeneration.¹ Another theory states that, once peripheral-nerve damage occurs, changes in the central nervous system affect a patient's sensory perceptions.⁴

Other studied causes of neuropathy include microvascular insufficiency, deficiency of nerve-growth factor and a lack of qualitative expression of the laminin B₂ gene.¹ Despite all the variations of etiology, patients share similar complaints regarding their sensations, including spontaneity of pain, continuity of pain and paroxysmal pain (shooting pain).⁵ A better understanding of neuropathic pain may lead to more effective treatments.

Clinical Presentation

Patients diagnosed with neuropathy present with variable degrees of pain and sensations. Clinicians are dependent on a patient's perception of pain to accurately assess his/her condition.⁶ Generally, patients will describe their pain as "electric," "jabbing," "deep aching" or "squeezing." Sometimes patients use words that describe temperatures such as *frostbite* or *burning*. Frequently patients do not describe these sensations as "pain" but instead as "tingling" or feeling like "pins and needles." These sensations are also described as worsening at certain times of the day or being provoked by certain activities.⁴ Verbal rating of the pain along with pain questionnaires can be used to measure the neuropathy.⁶ Diagnosis is made

Caroline J. Hodges, RPh

Thomas H. Jones, RPh

Tom Jones Drugs Health and Wellness Center, Garner, NC

David L. Willoughby

Campbell University School of Pharmacy, Buies Creek, NC

TABLE I. DRUGS FOUND TO BE EFFICACIOUS IN TREATING DIABETIC NEUROPATHY.

Analgesics	Aspirin, ibuprofen, sulindac
Anticonvulsants	Gabapentin, carbamazepine, phenytoin
Tricyclic antidepressants	Imipramine, amitriptyline, desipramine
Others	Ketamine, capsaicin, lidocaine

Adapted from Fedele D and Giugliano D.²

by physical assessment, including a neurological exam. Some ancillary tests, including electromyography, nerve-conduction studies and quantitative sensory testing, can confirm the diagnosis.⁴

Neurological examination is also a key component in the diagnosis of diabetic neuropathy. Two techniques used frequently are allodynia and hyperpathia. Allodynia is described as eliciting a painful response from a stimulus that does not normally invoke pain. Allodynia is still debated because it is hard for clinicians to agree on a definition of a "normally painful stimulus." *Hyperpathia* is a term used to describe an increased painful response to a stimulus that normally invokes pain.⁷ In addition to these sensory examinations, patients undergo a physical exam to determine a pattern of sensory dysfunction, with or without dysfunctional motor skills.⁴

Management of Pain

Glycemic Control

The management of pain begins with glycemic control in diabetic patients. Studies such as the Diabetes Control and Complications Trial have shown that patients achieving normoglycemia can slow the progression of diabetic neuropathy and maintain normal nerve function.^{6,8} Aside from glycemic control, pharmacological agents are used to treat diabetic neuropathy. Examples of drugs used in the treatment of diabetic neuropathy are listed in Table 1. Short-term therapy would include analgesics such as ibuprofen (600 mg four times a day) or sulindac (200 mg twice a day). These agents should be used with caution due to their risk of nephrotoxicity.⁸

Tricyclic Antidepressants

Tricyclic antidepressants have also been used to relieve neuropathic pain. Imipramine and amitriptyline have proven in various

Corresponding author: Caroline J. Hodges, RPh, Tom Jones Drugs Health and Wellness Center, 107 Vandora Springs Road, Garner, NC 27529

CASE REPORTS

CASE 1

A 58-year-old woman with a history of type 2 diabetes mellitus for 31 years presented with numbness and tingling sensations in both legs, burning sensations in her hands and fingers and a jabbing pain in her hip. Her current medications were lispro insulin and captopril 100 mg twice daily. She denied taking any medications for pain.

Before treatment she described her pain as an "8" on a ten-point scale. She began using the gel for her pain. At day three, she described that, an hour after administering the gel, the severity of pain decreased to a "6," with a two-hour duration of analgesia. At a week's follow-up, she experienced the same degree of pain relief.

CASE 2

A 75-year-old man with a history of type 2 diabetes for 14 years presented with a burning sensation in both feet. Past medical history was significant for a right hip replacement, with a resulting drop foot on the same side. The patient was unclear whether his drop foot was due to surgery or poor glycemic control. His current medications included insulin, metformin, azulfidine and diclofenac sodium with misoprostol.

Before treatment, the patient described his pain as a "3" or "4" on a ten-point scale. After three days of using the gel, he described the severity of pain as dropping to a "2" or "3," with a duration of analgesia of about eight hours. At a week's follow-up, he reported the same degree of analgesia.

CASE 3

A 75-year-old man with a history of type 2 diabetes for seven years presented with extreme pain and burning in his feet. His current medications included troglitazone 600 mg daily, amitriptyline 10 mg three times daily, hydrocodone 10 mg with acetaminophen 325 mg, trazodone, clonazepam, nisoldipine, hydrochlorothiazide and valsartan. Before treatment he described his pain as a "10" on a ten-point scale. He began using the gel every eight hours as needed for pain. At day three, he achieved a reduction in his pain, a "6" on a ten-point scale. In addition, he was able to begin using the gel only at bedtime to achieve pain relief throughout the night. After a week, he described the same amount of pain reduction.

controlled clinical trials to be superior to placebo.^{8,9} The exact mechanism of action is unknown.⁸ It is believed that tricyclic antidepressants work by the inhibition of both serotonin and norepinephrine. These drugs have been shown to be efficacious at one half to one third of the antidepressant dose, and onset of action for analgesia was quicker than for antidepressant activity.¹⁰ The lower dose allows for a lower side-effect profile; but side effects still exist, including dry mouth, constipation and cardiac side effects.¹¹

Anticonvulsants

Anticonvulsants can be an adjunct to therapy when tricyclic antidepressants do not adequately control the pain. The mechanism of action for these agents is the stabilization of membranes. Success has been reported with some drugs in this class; however, gabapentin may be the best choice because blood counts are not necessary as with other anticonvulsant agents.^{10,12}

Ketamine

The use of ketamine transdermally in a PLO has shown some promise in the treatment of neuropathy. Ketamine is an N-methyl-D-aspartate receptor antagonist and thus blocks a cascade of intracellular events that inhibit the hyperexcitability of spinal cord neurons. Animal data show that certain spontaneous pains and allodynia have been treated successfully with ketamine. Also, in humans, phantom limb pain has been treated with success.⁵ Ketamine has been used experimentally to treat neuropathic pain by a variety of routes including the intravenous and subcutaneous. Due to

some intolerable side effects associated with administration by these routes, transdermal application seems optimal.¹⁰ The PLO gels have been used for many years to deliver certain drugs transdermally. The topical form of ketamine is effective in treating painful neuropathy when other traditional medicines have failed.¹³

Autonomic Agents

Autonomic agents such as clonidine (an α_2 -agonist) and baclofen (a muscle relaxant) have been used as adjunctive therapy for neuropathy. Both agents may increase γ -aminobutyric acid activity, which inhibits neurotransmitters. Due to conflicting data concerning their analgesic effects, the use of these medicines has not gained wide acceptance for neuropathy.¹⁰

Our case reports involve the use of ketamine in a PLO gel in combination with gabapentin, amitriptyline, clonidine and baclofen. Because of the side-effect profiles of all agents included, it was decided to use them transdermally at the site of pain. The formula used was ketamine 10%, gabapentin 6%, baclofen 2%, amitriptyline 2% and clonidine 0.1%.

Conclusion

The management and treatment of pain associated with diabetic neuropathy are a challenge. Medications administered by transdermal gels are a viable option and potentially the most rewarding for a compounding pharmacist. Not only are we able to provide some pain relief in most situations, but we are also able to achieve this with a reduction in the usual side effects. Indeed, the real

challenge is whether the patient should begin with the polymedicine formula, as in our case reports, or with ketamine 10% and amitriptyline 2%, with additional ingredients simply added as needed to determine the optimal combination of medications for analgesic effects. Clearly, more research is needed to determine the best combination of agents. This is a long-term treatment regimen that would best be decided by the physician, compounding pharmacist and patient in each individual case.

References

1. Vinik A. Diagnosis and management of diabetic neuropathy. *Clin Geriatric Med* 1999;15:293-297.
2. Fedele D, Giugliano D. Peripheral diabetic neuropathy: Current recommendations and future prospects for its prevention and management. *Drugs* 1997;54:414-420.
3. Diabetes Control and Complications Trial Research Group. The effect of intensive diabetes therapy on the development and progression of neuropathy. *Ann Intern Med* 1995;122:561-568.
4. Galer BS. Neuropathic pain of peripheral origin: Advances in pharmacologic treatment. *Neurology* 1995;45(Suppl 9):17-24.
5. Nadine A, Bouhassira D. Mechanisms of pain in peripheral neuropathy. *Acta Neurol Scand* 1999;(Suppl 173):12-24.
6. Benbow SJ, Cossins L, MacFarlane IA. Painful diabetic neuropathy. *Diabet Med* 1999;16:632-644.
7. Serra J. Overview of neuropathic pain syndromes. *Acta Neurol Scand* 1999;(suppl 173):7-11.
8. Emanuele NV, Emanuele MA. Drugs to treat the tissue complications of diabetes: Peripheral neuropathy. *Comprehensive Therapy* 1995; 21:579-582.
9. Kingery WS. A critical review of controlled clinical trials of peripheral neuropathic pain and complex regional pain syndromes. *Pain* 1997;73:123-139.
10. Lipman AG. Analgesic drugs for neuropathic and sympathetically maintained pain. *Clin Geriatric Med* 1996;12:501-514.
11. Bonezzi C, Demartini L. Treatment options in postherpetic neuralgia. *Acta Neurol Scand* 1999;(Suppl 173):25-28.
12. Rosner H, Rubin L, Kestenbaum A. Gabapentin adjunctive therapy in neuropathic pain states. *Clin J of Pain* 1996;12:56-58.
13. Crowley KL, Flores JA, Hughes CN et al. Clinical application of ketamine ointment in the treatment of sympathetically maintained pain. *International Journal of Pharmaceutical Compounding* 1998;2:122-127. ■



Your guide to quality raw materials
Supplying compounding pharmacists worldwide

Special order items

 **triButyrate®**
 (Sodium) PHENYLBUTYRATE

 **triAcetate®**
 (Sodium) PHENYLACETATE

Amino Acids

 **L-Citrulline**  **L-Glutamine**

Visit our Websites: www.triplecrownamerica.com & www.tributyrate.com

To place an order, or for more information, call:

(215) 453-2500

triple crown america, inc., 13 North Seventh Street, Perkasie, PA 18944 USA • Fax: (215) 453-2508 • Email: info@triplecrownamerica.com