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Capsaicin: A Therapeutic Option for Painful Diabetic Neuropathy

Karen M. Basha, BSN, RN, CDE,* and Fred W. Whitehouse, MD*

Fifteen patients with diabetes mellitus who had painful diabetic neuropathy (PDN) were enrolled in a double-blind study to test the safety and efficacy of capsaicin 0.075% (Axsain, Genderm, Northbrook, IL). Twelve of the 15 patients completed the eight-week study. Nine of the 12 patients reported symptomatic relief; of these nine, five used the drug and four used the vehicle. The three patients who reported no relief of symptoms applied the vehicle. Capsaicin is potentially effective when burning pain is a major symptom of PDN. The side effects of capsaicin were limited and minimal. This agent should be considered by clinicians for treatment of PDN. (Henry Ford Hosp Med J 1991;39:138-40)

Diabetes mellitus (DM) affects more than 12 million people in the United States and its complications are the third leading cause of death today. All individuals with DM are susceptible to the numerous complications of this disease.

The macrovascular and microvascular complications of DM may lead to progressive end-organ involvement, the most painful of which is neuropathy. Clinical manifestations of painful diabetic neuropathy (PDN) include severe burning of the lower limbs and feet with nocturnal intensification (often occurring in a stocking-glove distribution), paresthesia, intermittent sharp or stabbing pains, anorexia, weight loss, and depression (1). Of those with either long-standing insulin-dependent diabetes mellitus (IDDM) or noninsulin-dependent diabetes mellitus (NIDDM), 50% will be affected by some form of neuropathy (2).

Treatment of PDN includes biochemical control of the diabetic state and appropriate pharmacologic therapy for symptomatic relief. A variety of pharmacologic strategies are available including oral medications, such as nonopioid anodynes, tricyclic antidepressants, phenytoin, and vitamin B (use of some of these may be limited by systemic side effects), and local physiotherapeutics, such as transepidermal neural stimulation ("TENS"). Aldose reductase inhibitors are currently being studied, but no consensus yet exists on their efficacy and safety.

Capsaicin (Axsain, Genderm, Northbrook, IL), a recently marketed topical agent, has been used with some success in post-herpetic neuralgia, post-mastectomy pain syndrome, and PDN. We participated in a multicenter Capsaicin Study Group and report our experience with this new agent in the treatment of PDN.

Pharmacology of Capsaicin

Capsaicin (trans-8-methyl-N-vanillyl-6-nonenamide) is an active ingredient found in many botanical species of the night-

shade family (Solanaceae). It is the chemical substance that makes hot peppers "hot." These plants were introduced in the 15th century in Europe where they were used as a food or condiment; they were also thought to have several medicinal properties. Capsaicin has also played a role in folk medicine, with its medicinal uses dating back to the 19th century. In recent years, this substance has been available in low concentrations and used in several over-the-counter preparations for arthritis (3).

As a topical cream, capsaicin is marketed in two strengths, 0.025% and 0.075%. The lower strength of capsaicin was initially advised for patients with post-herpetic neuralgia. Use of capsaicin, 0.075%, has recently been studied in clinical trials for the treatment of post-mastectomy pain syndrome and PDN. Its side effects include burning, stinging, and erythema at the site of application (which usually diminishes with repeated use), dry skin, and nasal inhalation irritant reactions. Capsaicin is thought to deplete substance P, a pain-modulating neurotransmitter, at the nerve terminals. Initial applications sensitize the nerve fiber membrane to release substance P, and continued use desensitizes the membrane which subsequently reduces local concentrations of substance P. Hence, the area of capsaicin application becomes less sensitive to pain. This decrease in pain is temporary but is sustained with repeated use of capsaicin (4). Studies suggest that when capsaicin is discontinued the depletion of substance P stops and symptoms return (5).

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LOCATION OF NEURALGIA

Body Area Affected: _____ (for Peripheral Polyneuropathy)

Dermatome Affected: _____ (for Radiculopathy)

BODY AREA CHART

PAIN SEVERITY

Check the **ONE** box that best describes the severity of the patient's pain during the time of day it is most intense.

None (0)	Slight (1)	Moderate (2)	Severe (3)	Very Severe (4)
[]	[]	[]	[]	[]

Fig 1—Dermatome chart used to record location of pain.

Multicenter Capsaicin Study Group

A total of 277 diabetic patients (136 IDDM and 141 NIDDM) with PDN were randomized to an eight-week, double-blind, placebo-controlled, multicenter clinical trial using either capsaicin or vehicle (placebo) to evaluate the clinical safety and efficacy of topically applied capsaicin cream (0.075%). Patients included 139 men and 138 women with a mean age of 60 years (range 27 to 81 years). The 12 medical centers across the United States participating in the study each randomized a mean of 20 patients (range 9 to 54) into one of the two groups.

The Henry Ford Hospital group enrolled 15 patients (9 female, 6 male) whose ages ranged from 48 to 79 years (mean 64 years). Eight patients had IDDM; seven patients had NIDDM. The duration of DM ranged from 6 months to 24 years (mean 12 years). Twelve of the patients had peripheral polyneuropathy and three had radiculopathy. The duration of the symptomatic neuralgia ranged from 2 months to 15 years (mean 4 years).

Inclusion criteria included: 1) individuals with IDDM or NIDDM between ages 18 to 85 years; 2) a fasting blood glucose < 180 mg/dL or a glycosylated hemoglobin < 11%; 3) presence of either clinical peripheral polyneuropathy or radiculopathy, characterized by local pain and paresthesia confirmed by findings on electromyogram (EMG); 4) pain interfering with daily activities and/or sleep at least some of the time; 5) other topical medications applied to the affected areas discontinued at least seven days prior to study entry; 6) all oral medications for pain associated with neuropathy continued but without change in dosage or frequency of administration; 7) medication prescribed for indications other than pain could be initiated provided their use did not interfere with the evaluation of the study drug. Informed consent was obtained from all participants in the study.

Exclusion criteria included: 1) females who were pregnant or lactating; 2) patients who had open lesions on the affected skin area; 3) individuals with a serious medical or psychiatric disease.

Before randomization at a pretreatment visit, the history was obtained and directed neurological examination performed.

PATIENT INSTRUCTIONS

1. Apply the medication cream to painful areas of your skin **FOUR TIMES A DAY** for the duration of the study. Even if pain stops, continue medication until your last visit to the clinic.

ALWAYS WASH YOUR HANDS AFTER APPLICATION OF THE CREAM. AVOID CONTACT WITH YOUR EYES AND WITH ANY OPEN WOUNDS OR IRRITATED SKIN WHEN APPLYING THE CREAM. KEEP OUT OF REACH OF CHILDREN.

2. When the drug is applied to normal skin, there may be mild to moderate discomfort and burning or stinging sensations, especially during the first week of treatment. Repeated application usually results in elimination or marked decrease of this discomfort. If you so choose, you may take two (2) tablets of aspirin or acetaminophen (e.g., Tylenol, Anacin-3, Datril), every four hours, for relief of the discomfort. However, if such discomfort is too distressing, you should call your doctor, and both of you will decide whether you should continue using the study medication.
3. Bring all used tubes of medication with you to your next scheduled visit.
4. Your doctor may consider making changes in your pain medications. If at any time, you make a change in the amount or type of medication you are taking, notify your doctor.
5. Your doctor will schedule the clinic visits for you as follows:
 - 2 weeks after your initial visit of the open label study
 - 8 weeks after your initial visit
 - then every 8 weeks, up to a total of one year on the study

Please contact your doctor at any time during the study if your pain worsens.

NOTE: Your doctor will also make a telephone follow-up call at 4 and 6 weeks after your initial visit.

6. Once you finish the study, your doctor will call you periodically to assess whether your pain has changed after discontinuation of the study medication.

Fig 2—Patient instructions for the application of study medication to the affected areas.

Nerve conduction was studied in patients who had not had the test in the previous six months. EMG, used at the onset of the study to confirm the diagnosis of PDN, was not repeated. The anatomical distribution of the pain was recorded on a dermatome chart (Fig 1).

Patients were randomly assigned into one of two study groups utilizing either capsaicin or a vehicle and were instructed to apply the cream to the affected area four times daily. Each patient was informed of the possible side effects of capsaicin and given an instruction sheet to follow (Fig 2). Instructions were reviewed and questions and concerns regarding the protocol were discussed with the patient prior to leaving the clinic.

The side effects of capsaicin included mild to moderate burning or stinging when applied to the affected area. If side effects occurred, patients were instructed to take two tablets of aspirin or acetaminophen every four hours. If symptoms were severe, patients were instructed to contact the clinic promptly to determine if the study drug should be discontinued. Each patient was also instructed to avoid contact with their eyes and mucous membranes when applying the cream and to wash their hands after each use. At baseline and at weeks 2, 4, 6, and 8, pain was assessed by the patient and nurse coordinator using three standard pain scales: physician global evaluation (PGE), visual analogue scale for pain intensity (VAS-P), and visual analogue scale for pain relief (VAS-R). The PGE was completed by the nurse coordinator and physician with input from the patient to assess changes in pain severity compared to baseline. The other two scales were completed by the patient. Patients were instructed to complete these questionnaires based on the time or times of the day the pain was most intense.

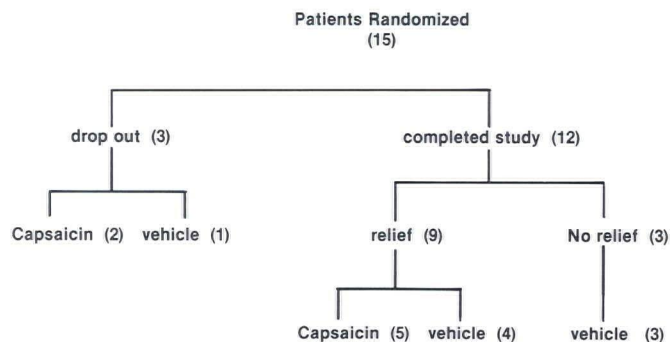


Fig 3—Schema for double-blind capsaicin study.

Results

Of the 15 patients enrolled in the Henry Ford Hospital group, seven used capsaicin and eight used the vehicle cream during the study period. Twelve patients completed the trial; of the three patients who dropped out, two did so because of severe burning (1 capsaicin, 1 vehicle) and one because of treatment failure (capsaicin). Nine patients reported moderate to complete relief of pain during the trial (5 capsaicin, 4 vehicle), and three patients reported no relief (all vehicle) (Fig 3).

Discussion

The results of the multicenter Capsaicin Study Group demonstrate that capsaicin offers symptomatic relief in the treatment of PDN and radiculopathy (6). These findings were based on the analyses of the efficacy parameters (i.e., PGE, VAS-P, VAS-R). Of the 277 patients randomized nationally, 138 received capsaicin and 139 received vehicle. Based on the final visit analyses of standard pain scales, 69.5% of the patients in the capsaicin group and 53.4% of the patients in the vehicle group reported improvement in pain (PGE) ($P < 0.012$). A total of 38.1% of the patients in the capsaicin group and 27.1% in the vehicle group reported a decrease in pain intensity (VAS-P) ($P < 0.037$). Finally, 58.4% of the capsaicin group and 45.3% of the vehicle group reported they had a relief of pain (VAS-R) ($P < 0.004$). All of these are significant at the 5% level (6).

In light of the overall findings of the multicenter group, we feel that capsaicin is worthy of consideration in the treatment of PDN. The placebo response, not uncommon in pain studies, can be attributed to the following factors: scheduled visits to talk with the patient regarding pain, patient response to the placebo effect, and rubbing the area skin with lanolin ointment which increases the local blood supply and is soothing to the skin.

Capsaicin is indicated in patients whose primary complaint from neuropathy is pain. Most patients whose symptoms improved with capsaicin reported burning pain as a primary complaint. The drug has not yet been studied in patients whose primary complaint is numbness or dysesthesia. A few patients with localized sensory mononeuropathy (intercostal and truncal neuropathy or meralgia paresthetica) may also benefit from its use. The goal of therapy, symptomatic relief, should occur two to six weeks after beginning therapy. Therapy is instituted with 0.025% capsaicin applied to the affected area four times daily. If no response is achieved, we advise the more concentrated form of 0.075% four times daily. Once relief is obtained, frequency of use can be adjusted to maintain symptom control according to individual need.

The advantages of capsaicin are: 1) application directly to the affected area, 2) no systemic effects, and 3) diminished local side effects with repeated use of the cream. Disadvantages include: 1) local side effects at the site of application, which, if severe, may require discontinuation of the medication; 2) high cost of treatment (\$53 to \$55 for a 45-gram tube of capsaicin at the 0.075% strength and an average of \$35 for a 45-gram tube at the 0.025% strength, with each tube permitting two to three weeks of therapy when used as advised); and 3) possible use without medical advice as patients may obtain it over-the-counter without a prescription. If local burning pain is a primary complaint of patients with diabetic neuropathy, the use of capsaicin merits a trial. Of course, this medication is not used in the presence of skin ulcers or infection. Although the results in our small sample of patients are not decisive, the multicenter report persuades us that the agent has therapeutic benefit. The frequency of relief by vehicle cream (in our experience as well as in the multicenter study) emphasizes the need for double-blind studies when assessing clinical effectiveness.

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