Treatment of Chronic Painful Diabetic Neuropathy With Isosorbide Dinitrate Spray

A double-blind placebo-controlled cross-over study

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OBJECTIVE — Considerable evidence implicates impaired nitric oxide (NO) generation in the pathogenesis of diabetic neuropathic pain. We therefore conducted a pilot study to examine the effects of isosorbide dinitrate (ISDN), a NO donor with local vasodilating properties, in spray form in the management of chronic neuropathic pain.

RESEARCH DESIGN AND METHODS — The study was of double-blind, randomized, placebo-controlled, and two-period cross-over design. After a 2-week run-in period, 22 diabetic patients (13 men, 20 with type 2 diabetes, age [mean ± SE] 63.7 ± 1.8 years, duration of diabetes 9.1 ± 1.5 years, duration of painful neuropathy 2.6 ± 0.4 years) were randomized to receive ISDN or placebo sprays for 4 weeks, exchanging their treatment for a further 4 weeks after a 2-week wash-out period. The patients administered the spray to both feet before bedtime. Biweekly pain and other sensory symptoms were assessed using a visual analog scale (VAS) and the Lickert scale, respectively.

RESULTS — ISDN spray reduced overall neuropathic pain ($P = 0.02$) and burning sensation ($P = 0.006$). No treatment difference was observed with other sensory modalities (hot/cold sensation, tingling, numbness, hyperesthesia, and jabbing-like sensation). At study completion, 11 patients (50%) reported benefit and wished to continue using the ISDN spray, 4 (18%) preferred the placebo spray, and the remaining 7 (32%) were undecided.

CONCLUSIONS — ISDN spray offers an alternative and effective pharmacological option in relieving overall pain and burning sensation in the management of painful diabetic neuropathy. The potential of ISDN spray in alleviating other specific sensory symptoms associated with diabetic peripheral neuropathy merits further study.

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Diabetic peripheral neuropathy, one of the most common late complications of diabetes, is frequently painful, with the pain involving predominantly the lower limbs (1,2). The pain may vary from mild tingling to deep-seated lancinating or severe unremitting pain. Night-time exacerbation of pain is common, with sleep deprivation and depression being common sequelae (3). The pathophysiology of the condition remains unclear, although it is associated with peripheral demyelination, a reduction in peripheral nerve conduction, and degeneration of myelinated and unmyelinated sensory fibers (4). Recent data suggest that impaired nitric oxide (NO) synthesis plays an important role in the pathogenesis of painful diabetic neuropathy. Sasaki et al. (5) and Rodella et al. (6) demonstrated that impaired neuronal NO generation in diabetic rats induced hyperalgesia, whereas Pitei et al. (7) showed that decreased NO production contributed to a reduction in endoneurial blood flow in type 2 diabetic patients with peripheral sensory neuropathy. The preservation of endothelial-dependent vasodilatory responses to nitroglycerin (8), which directly releases NO, further implicates a defect or defects in endoneurial NO synthesis as the cause of impaired vascular responses in diabetes. Although several studies have demonstrated that topical nitroglycerin can produce local vasodilation in the feet (9,10), no studies have looked at the effects of localized nitroglycerin application on painful diabetic neuropathy.

Speculating that impaired NO generation may play a role in diabetic neuropathic pain through defects in local vasodilation, we found that isosorbide dinitrate (ISDN) spray, a NO donor with potent local vasodilating properties, relieved some sensory symptoms, particularly pain and burning sensation, in a small number of our diabetic patients. We therefore conducted a pilot study to explore the analgesic effects of ISDN spray in patients with diabetic neuropathic pain. We specifically examined the effects of the spray in patients who were previously unresponsive or intolerant to conventional pain-relieving therapies.

RESEARCH DESIGN AND METHODS

Patients

Twenty-four patients were recruited to participate in the 12-week study. Two patients were excluded because they failed to attend follow-up after two visits; they were not included in analyses. The remaining 22 patients successfully com-

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Abbreviations: ISDN, isosorbide dinitrate; PVD, peripheral vascular disease; VAS, visual analog scale.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Patient characteristics*

Number of patients	22
Age (years)	63.7 ± 1.8 (41–76)*
Sex	13 males, 9 females
BMI (kg/m^2)	32.8 ± 1.4
Type of diabetes	2 type 1, 20 type 2
Duration of diabetes (years)	9.1 ± 1.5
Duration of neuropathy (years)	3.0 ± 0.5
Duration of neuropathic pain (years)	2.5 ± 0.4
Treatment order	10 ISDN, 12 placebo
HbA_{1c} (%)†	
At study entry	7.8 ± 0.3
At study completion	8.1 ± 0.4

*Data are *n* or means ± SE. Age range; †HbA_{1c} reference range 4.9–6.3%.

pleted the study. Patient characteristics are shown in Table 1.

All of the patients had difficult-to-treat symmetrical painful neuropathy. They had previously tried various analgesics, such as acetaminophen, and other specific therapies for neuropathic symptoms, such as amitriptyline or gabapentin; however, these had to be discontinued because the symptoms were unresponsive or the patients experienced unacceptable side effects. Eligible subjects included type 1 and type 2 diabetic patients not on any other medications for their neuropathic pain and with stable diabetic control. Exclusion criteria included erratic glycemic control, peripheral vascular disease (PVD) with absent foot pulses, presence of active foot ulceration, treatment with sublingual glyceryl trinitrate, male patients on concurrent sildenafil therapy for erectile dysfunction, neuropathic pain in upper limbs (affecting the patient's evaluation of pain), and the presence of other causes of peripheral neuropathies.

The pressure index ratio of ankle systolic pressure (mean of posterior tibial and dorsalis pedis) to brachial systolic pressure was >0.8 in each foot, and the foot pulses were palpable by two different investigators, thus excluding significant PVD as a cause of pain. Of the 20 type 2 diabetic patients, 9 were treated with insulin, 9 with oral hypoglycemic agents, and 2 with diet. No major changes in diabetic management had taken place during the 3 months before the study, and no therapeutic alteration was made throughout the study.

Possible side effects of the spray—e.g., palpitations, headaches, and faintness—were discussed with the patients before study entry. Informed consent was obtained from all the patients, and the study was approved by the local hospital ethics committee.

Study design and methods

Figure 1 demonstrates the study design. Patients attended at the beginning of the run-in period, where they were assessed neurologically, and then at biweekly intervals. The neurologic examination consisted of testing and grading of deep tendon reflexes, checking for sensory neuropathy using Semmes-Weinstein monofilament 5.07 (10 gram), vibration test using a Rydel-Seiffer graduated tuning fork, and general examination of the lower limb for foot deformity and ulcers. Venous blood samples were collected for the measurement of HbA_{1c} at baseline and study completion. Thyroid function tests, biochemical electrolytes, liver function tests, calcium profile, and B_{12}/folate levels were performed at baseline to exclude other causes of neuropathy. The HbA_{1c} assays were performed using the DCA 2000 analyzer (Bayer Diagnostics, Elkhart, IN). The coefficient of variation was 3.4% at the lower end of the range (mean 4.9%) and 4.2% at the upper end of the range (9.8%).

After the run-in period, the patients were reassessed neurologically and were randomly allocated to receive either placebo (40% propyline glycol in water) or 30 mg ISDN (Isocard) spray for 4 weeks. The patients and investigators were unable to distinguish ISDN from placebo sprays, as the containers were identical. The patients were asked to spray both feet with one actuation each (each actuation administers 30 mg of ISDN) before retiring to bed at night. After 4 weeks and a 2-week washout period, the patients exchanged their treatment for a further 4 weeks. A 10-cm visual analog scale (VAS) was recorded biweekly by the patients for pain, where 0 = no pain at all and 10 = the most severe pain ever experienced. Other neuropathic sensory symptoms (hot/cold sensation, tingling, numbness, hyperesthesia, jabbing-like sensation, and burning pain) were recorded as no symptom (0), mild (1), moderate (2), or severe (3) on a 3-cm Lickert scale. The treatment effect was defined to be the difference between the final score and the baseline score on the Lickert scale for each treatment phase. At the end of each treatment phase, patients were asked to record the likelihood of reusing the spray (very likely, very unlikely, and undecided).

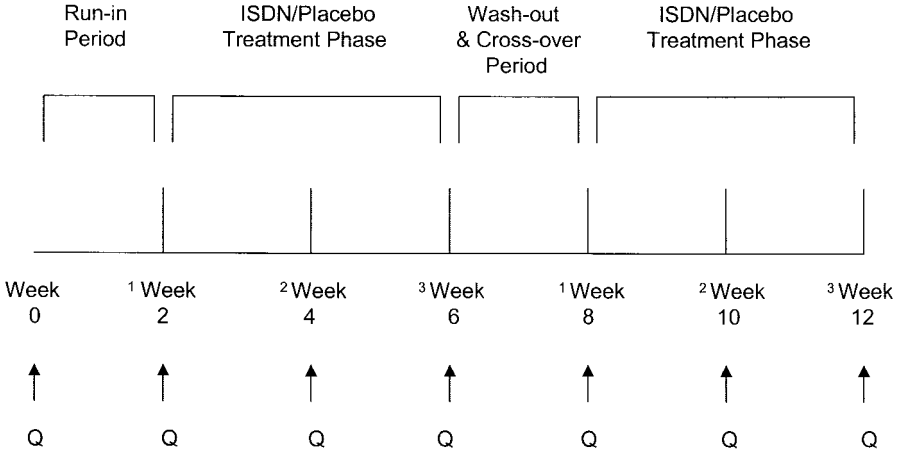

Figure 1—*Study design. For each treatment phase:* Q, *VAS assessment;* [1]*baseline assessment;* [2]*intermediate assessment;* [3]*final assessment.*

Table 2—*Mean VAS scores for each time point for overall pain with 25% and 75% quartiles*

Time point	Median VAS pain scores	Quartiles (25%, 75%)
Run in	5.5	5.0, 7.0
ISDN baseline	5.5	4.0, 7.0
ISDN intermediate	3.5	1.3, 6.0
ISDN final	3.5	1.3, 6.0
ISDN difference (final minus baseline)	−2.0	
Placebo baseline	5.0	4.3, 6.0
Placebo intermediate	5.0	3.0, 5.0
Placebo final	5.0	2.3, 7.0
Placebo difference (final minus baseline)	0	—

Difference between ISDN and placebo sprays, $P = 0.02$.

Statistical analysis

All statistical analyses were performed using SPSS for Windows (version 10.0; SPSS, Chicago, IL). Data are expressed as means ± SE. A carry-over effect was tested for by calculating the average of the two treatments and comparing the two treatment orders using a Mann-Whitney *U* test. Where there was no evidence of a carry-over effect, the patients with the two different orders were combined and the treatment effect was tested for using the Wilcoxon signed-rank test, since each patient had each treatment. Patients were only included in the analysis if they had symptoms on both placebo and treatment. *P* values <0.05 defined statistical significance.

RESULTS — During the ISDN phase of the study, two patients developed mild transient headaches, which resolved spontaneously and did not affect overall compliance with the spray. No local skin erythema was reported with ISDN or placebo sprays.

No significant carry-over effect for both ISDN and placebo sprays was observed, indicative of no residual effect when the sprays were discontinued. Significant reductions in pain ($P = 0.02$) (Table 2; Fig. 2) and burning sensation ($P = 0.006$) (Table 3) were observed using the ISDN spray compared with placebo. No significant differences were seen between the effects of the ISDN and placebo sprays in modifying other sensory modalities (Table 3).

There was no difference in the HbA_{1c} values, reflecting diabetic control, at study entry and on study completion (7.8 ± 0.3% vs. 8.1 ± 0.4%; $P = 0.14$). At study completion, 11 patients (50%) reported benefit and wished to continue using the ISDN spray, 4 patients (18%) preferred the placebo spray, and the remaining 7 patients (32%) were undecided.

CONCLUSIONS — Good glycemic control delays or prevents the onset of diabetic neuropathy (11,12) and ameliorates symptoms in those with acute painful neuropathy (13). However, even excellent glycemic control may be insufficient in some patients, particularly in patients with type 2 diabetes who often present with neuropathy when metabolic control appears satisfactory. Although the first steps in the management of diabetic painful neuropathy are to improve glycemic control and to use simple analgesics such as acetaminophen, additional drug treatment is frequently required (14). Tricyclic compounds, anticonvulsants, mexiletine, and topical capsaicin are often used, but many patients experience side effects (14). Our pilot study has demonstrated the efficacy of ISDN spray as an alternative pain-relieving agent for patients with resistant diabetic neuropathic pain.

All of our patients had continuous pain, worse nocturnally at baseline, and were previously unresponsive or intolerant to simple analgesics, antidepressants, anticonvulsants, or other pain-relieving measures. In addition to pain, all but two patients described unpleasant sensory symptoms such as "walking on pebbles." The worst-affected patients were more or less housebound and were unable to cope with daily chores due to the debilitating pain and sleep deprivation. Following nocturnal application of the spray, most of the patients who obtained benefit reported that the analgesic effect lasted through the following day, up until the next application of the spray. Some patients reported an increased exercise threshold, and one patient reported uninterrupted sleep at night, something she had not experienced for several years because of her painful neuropathy.

We speculate that the improvement in pain and burning sensation demonstrated with the ISDN spray in our study may be associated with the increased generation of NO, promoting vasodilation with secondary improvement in microvascular blood flow. Recently, several investigators have revealed vasa nervorum angiogenesis in diabetic rats following experiments using vasodilator therapy (15–17). The vasodilation induced by the increased generation of NO following ISDN treatment may induce angiogenesis

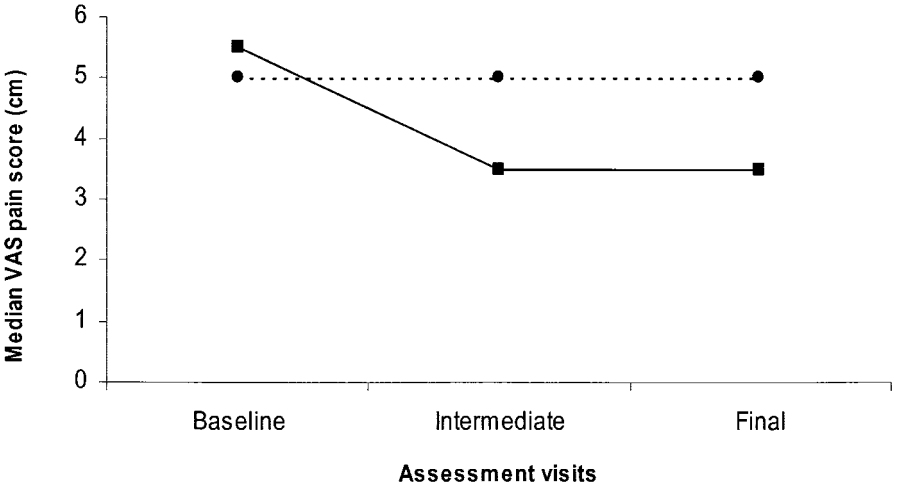

Figure 2—*Median VAS pain scores by assessment visits. ■, ISDN spray; ●, placebo.*

Table 3—*Number of patients experiencing other sensory symptoms and median Lickert scale scores (25% and 75% quartiles in brackets)*

	Symptom											
	Hot/cold		Tingling		Numbness		Hyperesthesia		Jabbing		Burning	
Time point	*n*	Median	*n*	Median	*n*	Median	*n*	Median	*n*	Median	*n*	Median
Run in	21	2.0 (2.0, 3.0)	20	2.0 (1.0, 2.0)	15	1.0 (0, 2.0)	11	0.5 (0, 2.0)	16	2.0 (0, 2.0)	19	2.0 (2.0, 3.0)
ISDN baseline	20	2.0 (2.0, 2.0)	19	2.0 (1.0, 2.0)	14	1.5 (0, 2.0)	11	1.0 (0, 2.0)	15	2.0 (0, 2.0)	20	2.0 (1.3, 2.0)
ISDN intermediate*	20	2.0 (1.3, 2.2)	19	2.0 (0.4, 2.0)	14	1.0 (0, 2.0)	11	0.5 (0, 2.0)	15	1.8 (0, 2.0)	20	2.0 (1.0, 2.0)
ISDN final*	20	1.6 (1.1, 2.0)	19	1.2 (0.7, 2.0)	14	1.0 (0, 2.0)	11	0.5 (0, 2.0)	15	1.6 (0, 2.3)	20	1.6 (1.1, 2.0)
Placebo baseline	20	2.0 (2.0, 2.0)	19	2.0 (1.0, 2.0)	14	1.5 (0, 2.0)	10	0 (0, 2.0)	15	2.0 (0, 2.0)	19	2.0 (1.0, 2.0)
Placebo intermediate*	20	2.0 (1.4, 2.8)	19	1.0 (1.0, 2.0)	14	1.5 (0, 2.0)	10	0 (0, 2.0)	15	1.8 (0, 2.5)	19	2.0 (1.0, 2.3)
Placebo final*	20	2.0 (1.4, 2.2)	19	1.2 (1.0, 2.0)	14	1.5 (0, 2.0)	10	0 (0, 2.0)	15	1.6 (0, 2.0)	19	2.0 (1.0, 2.5)
Treatment difference (final minus baseline) of ISDN and placebo sprays (*P* value)		0.06		0.52		0.89		0.18		0.94		0.006

*Median change in the Lickert scale scores at the intermediate and final assessment visit for each treatment phase, with reference to baseline scores.

of the vasa nervorum, and this may also explain the gradual increase in the analgesic effect of the spray by the end of the first week, which was sustained until treatment was discontinued.

Alternatively, the ISDN spray may have stimulated the light-touch afferent fibers to control pain, according to the spinal gate theory of Melzack and Wall (18). The theory states that activity generated by myelinated primary afferent fibers (A fibers) blocks the transmission of activity in the small unmyelinated C fibers. ISDN administered transdermally may have stimulated the light-touch peripheral receptors of the A fibers, thus suppressing neuropathic pain.

The lack of response of the other associated sensory modalities with the ISDN spray suggests that there may be other pathogenic factors involved. However, this apparent lack of response could equally be explained by the small number of patients with other sensory symptoms, the relatively short length of the study, the heterogeneity of the sample population, and the subjective evaluation of the symptoms.

In some diabetic patients, improvements in painful symptoms occur after control of hyperglycemia (19). No changes in diabetic management were made in this study, and HbA_{1c} remained steady throughout. There were no sex differences seen in the response to the ISDN spray.

We conclude that ISDN spray may be a new and useful addition to the management of patients with painful diabetic neuropathy with burning sensory symptoms. Our pilot study has shown that ISDN spray reduced pain and was associated with improvements in sleep, mobility, and mood. Although it may not be effective in all patients with diabetic peripheral neuropathy, it could be tried before resorting to other pharmacological agents, many of which may cause unpleasant side effects. Further studies with larger patient numbers are required to confirm the findings of this pilot study, determine whether the effects are sustained, and determine whether there are effects on other sensory symptoms associated with diabetic neuropathy. Nevertheless, even if the benefits are found to be short-lived, this knowledge may be of significant importance for the development of other therapies based on the NO hypothesis.

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