A Controlled Trial of Sorbinil, an Aldose Reductase Inhibitor, in Chronic Painful Diabetic Neuropathy

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SUMMARY

A double-blind, randomized, placebo-controlled crossover trial of the aldose reductase inhibitor sorbinil was undertaken in 15 patients (age 35–68 yr) with chronic painful diabetic neuropathy. Treatment was evaluated by subjective pain responses, clinical examination, vibration perception threshold, motor and sensory nerve electrophysiology, and cardiovascular reflex tests of autonomic nerve function. Among the many measurements, only pain, tendon reflex scores, and sural sensory potential amplitude improved significantly during sorbinil administration, while scores of clinical sensory examination deteriorated. Four patients experienced an idiosyncratic reaction that rapidly recovered on discontinuing the drug. This study suggests that aldose reductase inhibitor treatment with sorbinil may have an effect on symptomatic diabetic neuropathy in man.

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It has been suggested that the accumulation of sorbitol and fructose, which occurs in the nerves of diabetic persons,[1] may cause osmotic damage to Schwann cells[2] or endoneurial edema.[3] Aldose reductase is the rate-limiting enzyme in the polyol metabolic pathway from glucose to sorbitol, and aldose reductase inhibitors prevent[4] or reduce[5] sorbitol accumulation in the nerves and improve motor nerve conduction[6] of streptozotocin-diabetic rats. The only aldose reductase inhibitor previously reported in the treatment of diabetic neuropathy is alrestatin, which has low potency and a short plasma half-life.[7–9] Sorbinil (CP 45634, Pfizer), a more potent aldose reductase inhibitor,[5] has a completely different chemical structure and longer half-life.[10] In diabetic individuals without clinical symptoms or signs of neuropathy, oral administration of sorbinil reduces red cell sorbitol[11] and slightly increases nerve conduction velocity.[12]

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We report a double-blind, placebo-controlled, crossover study of sorbinil in 15 diabetic subjects with chronic painful diabetic neuropathy of ≥ 1 yr duration.

METHODS

PATIENTS

The inclusion criteria were (1) age less than 70 yr; (2) stable symptoms of painful neuropathy for longer than 1 yr; (3) clinical signs of peripheral sensory neuropathy; (4) exclusion of other causes of peripheral neuropathy, i.e., normal serum B_{12}, folate; normal plasma thyroxine, proteins, urea, and creatinine; no known malignancy; no history of alcohol abuse; and (5) no appreciable peripheral vascular disease, i.e., ankle pressure index >1.

Details of the 15 patients included are shown in Table 1.

The study was approved by the local Physicians' Advisory Ethical Committee, and all patients gave informed written consent. The duration of active treatment was limited to 28 days by the United Kingdom Clinical Trial Certificate.

TRIAL PROTOCOL

Each patient was studied for 16 wk and assessment was conducted on five occasions at intervals of 4 wk: at entry and at 4, 8, 12, and 16 wk. Each patient received two identical capsules once daily throughout the study. Placebo was given to all patients during weeks 1–4 and 13–16. During weeks 5–8 they received, randomly, either two 100-mg sorbinil capsules daily or identical placebo, and then the alternate capsules were given for weeks 9–12. The patients knew only that at least one treatment period would involve the active drug. Compliance was assessed by counting returned capsules and measuring plasma sorbinil concentrations. All patients continued their standard diabetic treatment and also any other medication being taken at the outset of the trial.

ASSESSMENTS

Symptoms. A standarized inquiry for symptoms of peripheral somatic and autonomic neuropathy was obtained at entry (Table 1). At each visit side effects were inquired for using a standard questionnaire.

TABLE 1
Details of patients at start of study

No.	Sex	Age (yr)	Duration of diabetes (yr)	Treatment*	Duration of pain (mo)	Autonomic symptoms†	Retinopathy‡	Proteinuria	Other diagnoses
1	M	46	22	I, D	60	I, GI, PH	B	—	—
2	M	60	11	O, D	120	I	P	—	—
3	M	58	15	I, D	18	I, PH	B	—	—
4	M	51	18	O, D	36	I, S	B	—	—
5	M	53	3	I, D	18	S	—	—	—
6	M	65	4	D	24	I, S	—	—	Myocardial ischemia Pernicious anemia (treated)
7	M	63	17	I, D	18	I, S	P	—	Hypothyroidism (treated)
8	M	60	3	O, D	26	I, GI, S	—	—	—
9	M	55	4	O, D	36	—	B	—	—
10	M	41	22	I, D	72	I, S	B	—	Duodenal ulcer
11	M	41	22	I, D	48	I, S	—	—	—
12	M	35	24	I, D	48	GI, PH, S	B	+	—
13	M	68	19	D	36	I, PH, S	—	—	Myocardial ischemia
14	F	61	15	I, D	30	PH, S	B	—	—
15	M	55	12	I, D	24	I, S	—	—	—

*D = diet, O = oral hypoglycemic agent, I = insulin.
†I = impotence, GI = gastric or bowel symptoms, PH = symptomatic postural hypotension, S = abnormal sweating.
‡B = background retinopathy, P = proliferative retinopathy.

Each patient kept a daily record of his pain symptoms both on a linear analogue scale and by choosing from a list of six descriptions of pain severity. At the end of each 4-wk treatment period each subject also made an overall assessment of treatment on the previous month's pain by choosing from seven further descriptions (Table 3).

Clinical assessment. A neurologic examination was conducted by the same observer (R.J.Y.) at entry and at the end of each treatment period, including assessment of touch (cotton wool), vibration (tuning fork 128 cps), pain (pinprick), temperature (cold piece of metal), and tendon jerks. A scored clinical evaluation based on the anatomic level below which, for each modality, sensory perception was impaired, and the ease of eliciting tendon jerks, was used to record changes.

Vibration perception threshold (VPT) was recorded bilaterally at the tip of the hallux and the medial malleolus using a hand-supported Bioaesthesiometer (Ohio Medical Supplies Limited). The tip of the probe was allowed to rest on the skin surface without additional pressure.

Electrophysiology. Bilateral measurements were carried out using a standard DISA 1500 Electromyograph, supramaximal stimuli, surface electrodes, and skin temperature maintained at 32°C as previously described.[13]

Autonomic function tests. Cardiovascular reflex tests of autonomic nerve function were performed as previously described in detail.[14]

Blood tests. At each visit hemoglobin and red cell indices, white cell count, platelet count, plasma urea, creatinine, sodium, potassium, calcium, phosphate, bilirubin, alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transpeptidase, alkaline phosphatase, glucose and glycosylated hemoglobin (HbA_1), and plasma sorbinil concentration were measured.

ANALYSIS OF RESULTS

Patient withdrawals and exclusions. Patients 2, 3, and 13 withdrew from the study because of side effects. Patient 14 also experienced side effects, but data relating directly to the crossover were complete and have been included in the analysis. Patient 6 was excluded because no appreciable plasma sorbinil levels were detected during the active treatment period, indicating probable noncompliance, although the conclusions did not alter when his data were included in the analysis.

Measurements of nerve function. Logarithmic and square-root transformations of some variables were used to normalize skewed distributions before statistical analysis.

Statistical computation. Differences from week 4 (baseline) values were computed for each period of active treatment forming the crossover and it was these differences (represented in tables as sorbinil-placebo) that were analyzed for each variable. The statistical analysis employed the method of Hills and Armitage in analyzing a two-period crossover.[15] Computations were also conducted for appropriate nonparametric analyses using the Mann-Whitney U test and Fisher's exact probability test.

RESULTS

Blood analyses. Glycemic control, as assessed by HbA_1, remained stable throughout the study in all patients; nor were there any significant changes in plasma urea, creatinine, electrolytes, proteins, or liver enzymes.

Adverse effects (Table 2). Four patients (nos. 2, 3, 13, 14) developed erythematous, itchy, macular rashes, three with oropharyngeal involvement including mucosal swelling and tenderness. These rashes resolved completely within 10 days of discontinuing the drug. Two patients also had hematologic changes (Table 2). Each had, contrary to instructions, continued medication in the presence of a rash. In both cases the hematologic abnormalities returned to normal within 7 days of stopping treatment. The cervical lymphadenopathy noted in one patient completely regressed 2 wk after discontinuing the drug. No patient without a rash developed any other symptoms on sorbinil.

TABLE 2
Adverse effects of sorbinil treatment

Patient	Time of onset of rash (days)	Description of rash	Oropharyngeal involvement	Hematologic effects	Hepatic toxicity
2	6	Itchy erythematous maculopapular over trunk and legs	0	Not known	Not known
3	16	Desquamating, erythematous, macular over scalp and face	+ + + Swollen tender mucous membranes. Painful to swallow	None	None
13	8	Generalized confluent erythematous, associated fever/myalgia, swollen hands and feet	+ + + Swollen tender mucous membranes. Painful to swallow	Transient leucopenia and thrombocytopenia	None
14	13 (adenopathy) 20 (rash)	Itchy erythematous macular over trunk, head, neck, and proximal limbs. One week previously developed marked cervical lymphadenopathy	+ Minimal discomfort on swallowing	Transient leucopenia	None

Symptomatic changes. The subjective overall pain assessments given by the patients at the end of each treatment period (Table 3) showed that improvement in pain was reported significantly more frequently ($P < 0.02$) by those taking sorbinil. When the patients' daily diary cards were considered, however, there was no difference in any of the scores during the active period.

Since the scores in Table 3 are based on how the patient felt in the previous 4 wk, it was considered statistically valid to perform a test of significance only on the data relating to the first crossover period (weeks 4–8). The patient with a rash who continued with medication was included and the patient who stopped treatment because of a rash was assigned a score of 0. Fisher's exact probability test then yielded a two-tailed probability of 0.014 that sorbinil is symptomatically effective. The scores when sorbinil was given in the second crossover period (weeks 9–12), after treatment with placebo had been ineffective, were similar (mean score on sorbinil first period, 1.4; second period, 1.6) and strongly support the above result.

Clinical measurement of peripheral somatic nerve function. Significantly higher scores for sensory impairment were seen on sorbinil ($P = 0.02$), implying deterioration, whereas significantly higher scores for reflexes, implying improve-

TABLE 3
Pain assessments at end of each treatment period

	Subjective overall symptom assessment*			
	Wk no.			
	4	8	12	16
Patient	Placebo	Sorbinil	Placebo	Placebo
2	0	Rash†	—	—
4	0	1	2	−1
5	0	0	0	−2
8	1	3	3	0
9	1	2	2	0
11	1	1	2	2
13	0	3/rash‡	—	—
	Placebo	Placebo	Sorbinil	Placebo
1	0	0	2	−1
3	0	0	Rash†	—
7	0	0	3	−2
10	−1	0	1	−2
12	1	0	2	2
14	0	0	1/rash‡	−2
15	0	0	0	0

Patient 6 was excluded because no sorbinil was detected in plasma.
*0 = no change from previous month, 1 = slight improvement, 2 = considerable improvement, 3 = complete relief, −1 = slightly worse, −2 = much worse.
†Rash caused withdrawal before 28 days of treatment completed.
‡Rash developed but patient continued treatment for 28 days.

TABLE 4
Measurements of peripheral somatic and autonomic nerve function—group means ± SE before and after sorbinil or placebo

Measurement	Group	Wk no. 4	Wk no. 8	Wk no. 12	Sorbinil-placebo (SE)	Significance
Sensory level score†	A*	12.67 (1.58)	12.0 (1.21)	16.17 (1.68)	3.08	P = 0.02
	B*	9.4 (1.12)	8.8 (1.2)	6.8 (1.53)	(1.09)	
Tendon reflex score†	A	17.5 (1.2)	17.67 (1.38)	18.17 (1.28)	1.33	P = 0.04
	B	16.4 (2.4)	18.67 (0.92)	17.4 (1.4)	(0.59)	
VPT hallux (V)‡	A	70.8 (12.17)	60.67 (14.77)	61.5 (10.38)	4.25	NS
	B	56.0 (16.87)	54.5 (15.7)	51.0 (12.99)	(2.92)	
VPT medial malleolus (V)‡	A	73.17 (10.57)	70.8 (11.44)	62.83 (11.97)	−0.3	NS
	B	58.2 (11.94)	53.4 (10.89)	51.6 (11.18)	(2.3)	
Median nerve MCV (ms^{-1})	A	47.07 (1.15)	46.44 (1.12)	47.47 (1.3)	0.89	NS
	B	44.24 (2.08)	44.9 (1.76)	44.14 (0.98)	(0.73)	
Peroneal nerve MCV (ms^{-1})	A	33.35 (2.24)	33.81 (2.47)	35.39 (2.1)	0.66	NS
	B	33.48 (1.36)	33.98 (2.18)	34.24 (1.51)	(0.66)	
Median nerve						
SCV (ms^{-1})	A	34.46 (2.29)	33.89 (1.49)	32.70 (1.69)	−1.02	NS
	B	33.31 (2.42)	35.32 (1.30)	34.37 (1.36)	(0.62)	
SPA (μV)	A	4.34 (0.59)	4.31 (0.81)	4.21 (0.52)	−0.04	NS
	B	4.06 (1.08)	3.22 (0.65)	3.18 (0.73)	(0.39)	
Sural nerve						
SCV (ms^{-1})	A	19.79 (1.92)	18.13 (2.31)	20.80 (2.28)	0.39	NS
	B	22.62 (2.36)	19.85 (2.60)	20.74 (2.21)	(1.19)	
SPA (μV)	A	11.93 (3.21)	9.65 (2.85)	14.56 (3.59)	3.73	P = 0.05
	B	5.31 (1.30)	8.84 (2.32)	6.29 (1.40)	(1.66)	
Valsalva ratio	A	1.11 (0.05)	1.11 (0.05)	1.19 (0.11)	0.02	NS
	B	1.42 (0.16)	1.33 (0.12)	1.37 (0.13)	(0.05)	
Lying-standing heart rate change (30:15 ratio)	A	1.02 (0.03)	1.02 (0.02)	1.01 (0.02)	0.00	NS
	B	1.03 (0.02)	1.10 (0.04)	1.09 (0.04)	(0.02)	
R-R interval variation with deep breathing (max-min HR—beats/min)	A	4.5 (4.0)	2.8 (1.0)	3.9 (2.0)	0.22	NS
	B	15.6 (5.0)	12.1 (4.0)	8.9 (3.0)	(0.29)	
Postural hypotension (systolic BP fall—mm Hg)	A	36.3 (11.0)	36.6 (7.0)	30.2 (8.0)	0.04	NS
	B	21.4 (7.0)	22.2 (7.0)	19.7 (8.0)	(0.45)	
Sustained handgrip (diastolic BP rise—mm Hg)	A	17.3 (3.0)	16.8 (2.0)	15.0 (3.0)	0.18	NS
	B	23.0 (4.0)	19.5 (2.0)	15.1 (4.0)	(0.29)	

*A: placebo week 5–8, sorbinil week 9–12 (N = 6); B: sorbinil week 5–8, placebo week 9–12 (N = 5).
†For scoring method see text.
‡Right and left measurements combined.

ment (P = 0.04), were also found during the active treatment period (Table 4). Although VPT values at the ankle were lower on sorbinil, the difference was not significant.

Peripheral somatic electrophysiology and autonomic function tests. Table 4 also details the peripheral somatic nerve and autonomic function results. The only significant change was that sural nerve sensory potentials were greater on sorbinil (P = 0.05). There were nonsignificant trends toward improvement in motor nerve conduction but deterioration in sensory nerve conduction during active treatment.

DISCUSSION

This study suggests that the short-term administration of sorbinil, an aldose reductase inhibitor, may partially relieve the symptoms of chronic painful diabetic neuropathy. Among many measurements of nerve function, the only significant objective changes were an improvement in reflex scores, an increase in sural nerve sensory potentials, and a deterioration in sensory scores in those receiving sorbinil. There were nonsignificant changes in vibration perception threshold and motor nerve conduction toward improvement, while sensory nerve conduction was slightly lower during active treatment.

Four patients experienced side effects. These comprised a rash with variable leucopenia and lymphadenopathy, which was reversible and resolved within 10 days of discontinuing the drug.

The symptomatic benefit was only apparent when monthly and not daily pain assessments were analyzed. Studies of analgesics in rheumatology have given rise to similar discordance between methods of assessing pain,[16] and it seems that a daily record, where the patient compares his symptoms with those of the previous 24 h, may be insensitive to slowly changing discomfort. A similar improvement of neuropathic symptoms has also been recorded in diabetic patients given the aldose reductase inhibitor alrestatin either in single-blind crossover[8] or in double-blind parallel group[9] studies.

Only three of the objective measurements (sensory threshold, reflex score, and sural sensory potential) showed changes that achieve statistical significance. If a larger number of variables are analyzed, occasional apparently significant results will, of course, appear by chance. Handelsman and Turtle[8] in a 4-mo single-blind trial of alrestatin in nine chronic neuropathic patients found no changes in nerve conduction velocities. Fagius and Jameson[9] studied the effect

of alrestatin for 3 mo in a heterogenous group of patients with and without clinical symptoms of neuropathy. A slight but significant improvement in objective sensory testing and variable electrophysiologic results were found in the active treatment group, although this was almost entirely restricted to their insulin-dependent patients. Furthermore, deterioration in the placebo group—rather than improvement in the active treatment group—seemed to account for many of the differences observed. In the only other reported study of sorbinil, in diabetic patients asymptomatic of neuropathy, a small but significant improvement in mean motor conduction velocity occurred.[12] Therefore, documented objective changes following administration of aldose reductase inhibitors have been small, variable, and largely confined to patients with probably less severe nerve damage than that of our subjects.

Nevertheless, as exemplified by the Guillain-Barre syndrome,[17] restored clinical function may proceed independently of electrophysiologic improvement in polyneuropathy. Indeed, because of protean factors influencing conduction velocity alone, it has been suggested that electrophysiology by itself is insufficient to evaluate improvement of chronic diabetic polyneuropathy.[9] Numerous factors are now implicated in the abnormal nerve function of diabetic neuropathy and it is recognized that appreciable subcellular and functional alterations may occur long before any clinically or physiologically detectable change.[18] Conceivably, the pain of diabetic neuropathy might be mediated by metabolic, rather than structural, damage.

We have thus demonstrated improvement in pain but only a few variable objective changes in nerve function during a short-term trial of sorbinil in chronic painful diabetic neuropathy. They support the hypothesis that the polyol pathway is implicated in the pathogenesis of diabetic neuropathy. Longer-term studies of sorbinil in patients with milder abnormalities may elucidate the role of abnormal polyol pathway metabolism in diabetic neuropathy.

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