

Sodium Valproate Drug Used in Painful Diabetic Neuropathy: A Randomized Double Blind Placebo Hospital Based Controlled Study

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ABSTRACT

Background: Various drugs are effective in the management of painful diabetic neuropathy, but none is completely satisfactory. We previously found sodium valproate to be effective and safe in a short-term study. The aim of this study to test the effectiveness and safety of sodium valproate in the management of painful diabetic neuropathy over 3 months.

Methods: Consecutive attending patients with type 2 diabetes mellitus with painful neuropathy were asked to participate in the trial: 48 agreed. Five were excluded: three with HbA_{1c} >11, one with too low a pain level and one who withdrew consent. The remaining 43 were given either drug (group A) or placebo (group B). Each patient was assessed clinically. Quantitative assessment of pain was done by McGill Pain Questionnaire, Visual Analogue Score and Present Pain Intensity, at the beginning of the study, after 1 month and after 3 months. Motor and sensory nerve conduction velocities were measured initially and after 3 months. Liver function tests and other adverse drug-related effects were assessed periodically.

Results: Of the 43 patients, four dropped out: one in group A and three in group B. There was significant improvement in pain score in group A, compared to group B, at 3 months

($p < 0.001$). The drug was well-tolerated by all patients, except one, who had raised serum AST and ALT levels after 1 month of treatment, and whose treatment was discontinued.

Conclusion: Sodium valproate is well-tolerated, and provides significant subjective improvement in painful diabetic neuropathy.


Keywords: Sodium Valproate, Type 2 Diabetes Mellitus, HbA_{1c}.

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INTRODUCTION

Diabetic neuropathy is defined as the presence of symptoms and/or signs of peripheral nerve dysfunction in a patient with diabetes, after the exclusion of other causes.' In the course of diabetes, some 20%90% of individuals eventually develop diabetic neuropathy.² The aetiological factors attributed to diabetic neuropathy can be grouped into those having a definite role (e.g. poor glycaemic control, duration of disease) and those with a probable added influence (e.g. hypertension, age, smoking, hyperinsulinaemia, dyslipidaemia).¹⁻⁷

Painful diabetic neuropathy requires medical attention because of its adverse effect on quality of life. The important drug interventions in its management include non-steroidal anti-inflammatory drugs (NSAIDs), anti-depressants and anti-epileptic drugs," but there are problems with side-effects and contraindications for all these drugs. Other drugs used for pain relief have include clonazepam, gabapentine, lamotrigine, baclofen, i.v. lidocaine or mexiletine, aldose reductase inhibitors, gammalinolinic acid, nucleosides, nerve growth factor and capsaicin-containing ointments, but none is entirely satisfactory.

Sodium valproate, which has proved to be effective in trigeminal neuralgia and migraine prophylaxis,' has also shown significant role in the subjective improvement of painful diabetic neuropathy, with a unique advantage of low toxicity and favourable side effect profile." In an earlier study," we observed a significant subjective improvement in painful diabetic neuropathy in patients receiving sodium valproate in comparison to placebo at the end of one month. Because that was a short-term study, we began a fresh one in January 2002 to study the usefulness and safety profile of this drug over a longer period in the management of painful diabetic neuropathy.

MATERIALS & METHODS

Patient and Control Selection

A consent form explaining the nature of the study in detail was given to consecutively attending patients of diabetes mellitus with painful neuropathy, and the first 48 patients were included in the trial and asked to attend on a specific date. Five patients were not included in the study: three had HbA_{1c} > 11, one had too low a pain

score (Visual Analogue Scale <4), and one patient withdrew consent; thus 43 patients were followed up for 3 months. The medications offered to the patients were given in packets containing sufficient drug to last for 3 months, bearing a distinctive code number. All patients were subjected to thorough interview, clinical examination and relevant laboratory investigations. All were asked to fill in (by themselves or with assistance) a short-form McGill pain questionnaire (SF-MPQ), visual analogue score (VAS) and present pain intensity (PH), first initially, then after 1 month and then 3 months. Biochemical examinations, which included urinalysis, fasting blood sugar, HbA_{1c}, lipid profile and liver function tests (serum bilirubin, AST, ALT) were done at the beginning of the study. Liver function test and blood sugar were studied on every subsequent visit to check glycaemic control and to rule out any hepatotoxicity of sodium valproate.

Depending on the specific code number, the patients received either 500 mg (one tablet) of sodium valproate once a day, or similar type of placebo one tablet once a day. At the end of one week, leading questions were asked for sodium valproate toxicity in the form of nausea and vomiting, and the patients were examined for detailed neurological examination, specially nystagmus and ataxia. Serum AST/ALT was done in all the patients, and patients having normal values were subsequently put on one tablet two times a day for remaining three months. Patients who showed signs of intolerance did not continue in the study.

All the data, along with code numbers, were submitted to the statistician, and after decoding, the patients were divided into group A (receiving drug) and Group B (receiving placebo). All patients were kept euglycemic by diet alone, OHA, OHA + insulin or insulin alone. None of the patients were allowed to take analgesics for control of pain.

Selection Criteria

1. Diabetes for at least 6 months on stable dosage of insulin or oral hypoglycemic agent and having reasonable diabetic control (HbA_{1c} <11).
2. Daily neuropathic pain of at least moderate severity for > 3 months, which interfered with daily activity or sleep.
3. Pain intensity of > 4 on a visual analogue pain scale.
4. Written consent to participate in the study.

Exclusion Criteria

Patients suffering from liver disease, pulmonary tuberculosis, thyroid disorders, uraemia, vitamin deficiency, hereditary and paraneoplastic neuropathy, alcoholism, or patients on steroid therapy, were not included after relevant clinical and biochemical examination.

Laboratory Studies

Fasting blood sugar estimation was by the glucose oxidase method. Glycated haemoglobin (HbA_{1c}) of each patient was measured by high-performance liquid chromatography.

Table 1: Baseline characteristics

Baseline	Group A (Drug) (N=21)	Group B (Placebo) (N=18)	P-value
Mean Age (yrs)	54.38±8.77	56.24±8.75	0.496
Sex (M:F)	4:3	1:1	
Duration of type 2 Diabetes (Yrs)	8.85±4.18	8.80±3.84	0.969
BMI	24.43±3.76	24.30±3.07	0.901
Weight/height ratio	0.93±0.08	0.91±0.08	0.0641
A/B index	0.89±0.10	0.91±0.09	0.590
HbA1C (%)	8.78±1.26	8.58±1.10	0.587
FBS (mg%)	148.19±22.30	151.7±1.1.	0.620
Dyslipidemia	30%	50%	0.435
Microalbuminuria	28.58%	22.22%	0.733
Retinopathy	30%	27.78%	0.734

Table 2: Changes in pain score

Parameters	Sodium Valproate (N=21)			Placebo (N=18)			P –value (Drug v/s placebo at 3 months)
	Baseline	1 month	3 months	Baseline	1 month	3 months	
5F-MPQ	19.47±6.79	12.95±5.41	9.66±5.96	17.76±5.23	18.86±5.47	17.88±5.42	<0.0001
VAS	6±1.95	3.95±1.74	3±2.12	5.71±1.70	6±1.84	6±1.84	<0.0001
PPI	2.71±1.0	1.71±0.84	1.33±0.66	2.57±0.92	2.67±0.90	2.61±0.91	<0.0001

RESULTS

Our study showed that the demographic profile of patients in table no. 1. Changes in pain score from baseline to end of treatment (assessed by SF-MPQ, VAS and PPI) are shown in Table 2. Differences between sodium valproate and placebo group were significant at the endpoint for all three scores, both at the end of

one month and after three months. In group A (the drug group), initial mean SF-MPQ was 19.47 ± 6.79, falling to 9.66 ± 5.96 (p<0.001) after 3 months. Similarly, mean VAS fell from 6 ± 1.95 (baseline) to 3 ± 2.12 (3 months) (p<0.001), and mean PPI from 2.71 ± 1.00 (baseline) to 1.33 ± 0.66 (3 months) (p< 0.001).

DISCUSSION

Painful diabetic neuropathy significantly affects the quality of life, so far no ideal drug has been available for its management. In the absence of curative therapy, the main aim of management is to provide symptomatic pain control using pharmacological and non-pharmacological agents, and to preserve good glycaemic control. Pharmacological therapy includes tricyclic antidepressant, narcotic analgesics, anticonvulsants and anti-arrhythmic drugs, but adverse effects have limited the effectiveness of these agents.⁹ Double-blind trials of the tricyclic antidepressant amitriptyline have demonstrated significant benefits in reducing burning, aching, sharp, throbbing, and stinging pain. "This dose-dependent effect is independent of mood elevation" However, the use of amitriptyline in patients with heart block, urinary tract obstruction, orthostatic hypotension, or narrow-angle glaucoma, is contraindicated. Diphenylhydantoin which is commonly used in the management of painful neuropathy,² was found to be of no significant value in a double-blind crossover study." In three controlled, double blind studies, carbamazepine was shown to be of value in painful diabetic neuropathy, but because its potential toxicity, its use is limited: Other drugs in use for pain relief are clonazepam, baclofen, i.v. lidocaine or mexiletine, aldose reductase inhibitors, gamma linolenic acid, nucleosides, nerve growth factors and capsaicin containing ointment.¹⁴⁻²¹ The use of these drugs for long duration in painful diabetic neuropathy is limited because of their adverse side effects. Capsaicin-containing ointments produce initial irritation, which is too unpleasant for continuous use." Gabapentin has been shown to be more effective than placebo in doses ranging from 900 to 3600 mg/day.²³ The lower end of this dose range may be relatively ineffective. The main side-effects of gabapentin are dizziness, somnolence, headache, diarrhoea, confusion and nausea.²³ We previously observed a significant subjective improvement in painful diabetic neuropathy in patients receiving sodium valproate in comparison to placebo at the end of one month,¹¹ and unlike other anti-epileptic drugs, it has a favourable side effect profile.⁹ This study tested the efficacy and safety of sodium valproate over a period of 3 months. At the end of the study, there was a statistically significant reduction in pain score values (SF-MPQ, VAS and PPI) in patients treated with sodium valproate, compared to placebo. Motor and sensory nerve conduction velocities, which were deranged the beginning of study in diabetic patients of both group showed no improvement after 3 months. Similar findings were observed in the earlier study.¹¹

CONCLUSION

We concluded that the useful role of sodium valproate in the management of painful diabetic neuropathy, assessed by three different pain score (Sf-MPQ, VAS and PPI), and the drug was well tolerated by our patients.

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