Yamanashi Med. J. **12**(2), 45~51, 1997

The Effects of Epalrestat on Subjective Symptoms and Vibratory Threshold in Type 2 Diabetic Patients with Neuropathy

Masato TAWATA, Kaoru AIDA, Masaharu INOUE, Akihiro KURIHARA, Eiichi IWASE, Naoya GAN, and Toshimasa ONAYA

The Third Department of Internal Medicine, Yamanashi Medical University, Tamaho, Yamanashi 409-38, Japan

Abstract: We evaluated the effects of epalrestat on subjective symptoms and vibration sensation in type 2 diabetic patients with neuropathy. The patients were administered epalrestat 150 mg/day orally in three divided doses for 3 months (treatment period), and the agent was discontinued for 3 months (washout period). Epalrestat relieved numbness in 12 of 16 patients after the treatment period, and numbness worsened in 5 of 11 patients after the washout period. Chi-square analysis revealed significant effects of epalrestat on numbness ($p<0.001$) and also on other symptoms ($p<0.05$). Vibration sensation was evaluated by measuring vibratory threshold using an SMV-5 vibrometer. The vibratory threshold significantly decreased in the upper ($p<0.05$) and the lower ($p<0.01$) extremities after the treatment period and increased in the lower extremity ($p<0.05$) after the washout period by paired t-test. There was no significant change in glycosylated hemoglobin as a whole during the study. These observations confirm that epalrestat relieves subjective symptoms and improves vibration sensation in type 2 diabetic patients with neuropathy without affecting glycemic control.

Key words: Epalrestat, Aldose reductase inhibitor, Diabetic neuropathy, Vibratory threshold, SMV-5 vibrometer

INTRODUCTION

The incidence of diabetic complications such as neuropathy, retinopathy and nephropathy has increased as the life expectancy of diabetic patients has lengthened due to the progress in glycemic control. Diabetic neuropathy involves a variety of clinical manifestations such as mononeuropathy, autonomic neuropathy and peripheral polyneuropathy, with the latter being the most common[1]. So far, vascular[2-5] and metabolic[6,7] hypotheses have been proposed as the etiology of diabetic neuropathy. However, neither its etiology nor the treatment has been established. The introduction of aldose reductase inhibitors offers some hope of treating diabetic neuropathy as well as other diabetic complications[8]. In Japan, the aldose reductase inhibitor epalrestat is commercially available and has been reported to be effective on diabetic neuropathy by Goto *et al.*[9]. However in their study, the differences in nerve function tests between epalrestat and placebo are small. So, we wanted to confirm the efficacy of epalrestat by another method.

On the other hand, Suzuki *et al.*[10,11] developed SMV-5 vibrometer which quantifies vibration sensation by measuring vibratory threshold. We previously reported that measuring vibratory threshold by an SMV-5 vibrometer was a better parameter than measuring nerve conduction velocity in the evaluation of the effects of prostaglandin $E_1 \cdot \alpha CD$[12] or lipo-prostaglandin E_1[13] on diabetic neuropathy. We also reported the effectiveness of Goshajinkigan on vibratory threshold measured by an SMV-5 vibrometer on diabetic neuropathy[14]. In the present study, we investigated the effects of epalrestat on subjective

Received February 17, 1997
Accepted March 31, 1997

symptoms and on vibration sensation by measuring vibratory threshold with an SMV-5 vibrometer in type 2 diabetic patients with neuropathy.

Subjects and methods

Subjects: We randomly selected 19 type 2 diabetic patients who had been regularly visiting the outpatient clinic of our hospital. There were 8 males and 11 females aged 43 to 79 years old (mean 62.1 years). They had suffered from diabetes mellitus for 5 to 30 years (mean 12.9 years). The diagnosis of diabetic peripheral neuropathy was based on the consistent complaints of numbness, cold sensation or pain, and on the objective findings of diminished or loss of deep tendon reflexes and increased vibratory threshold. Excluded from the study were patients with peripheral neuropathy due to toxic or metabolic cause other than diabetes mellitus, endocrinological and viral disorders or cancers. Patients who had been taking agents such as vitamin B_1, B_6, B_{12} or E, prostanoids, cilostazol, kampo medicines, antidepressants or tranquilizers were also excluded from the study. This study was performed in accordance with the principles of the Declaration of Helsinki in which all patients gave their full informed consent to participate.

Drug: Epalrestat, 5-[(1Z, 2E)-2-methyl-3-phenylpropenylidene]-4-oxo-2-thioxo-3-thiazolidineacetic acid, Kinedac™ (CAS 82159-09-9), is a product of Ono Phamaceutical Co. Ltd.(Osaka, Japan). Its batch designation in Japan is No. 873999.

Designs: Patients were evaluated for their subjective symptoms by questionnaires and the vibratory threshold twice with the interval of one month before the study. Then the patients were administered epalrestat 150 mg/day orally in three divided doses for 3 months (treatment period), and the agent was discontinued for 3 months (washout period). The subjective symptoms and the vibratory thresholds were evaluated every month during the study period. Epalrestat was then restarted in 9 patients after the washout period.

Subjective symptoms were classified as numbness (spontaneous abnormal sensation or shibire sensation), pain, cold sensation and paresthesia (abnormal sensation upon touching). The patients were asked to complete questionnaires rating their respective symptoms on a scale of "0" to "3" every month throughout the study period. The scale of the symptoms were defined as the followings: 0, no symptom; 1, slight; 2, moderate; 3, severe. The questionnaires were collected at the end of the study period. Symptom scores at the end of each period were adopted, and compared to those of the preceding periods. "Improved" or "worsened" in subjective symptoms were defined when symptom scores showed a reduction or an increase more than 1 point, respectively, compared to those of the preceding period. Those whose symptom scores were "0" before the study were excluded from the statistical analysis.

Vibratory threshold was measured by an SMV-5 vibrometer (Teknolog, Tokyo, Japan) at the styloid process of ulna in the upper extremity and at the medial malleolus of tibia in the lower extremity, following 5 min of bed rest. Measurements were repeated four times, and the mean of the last three was taken as the vibratory threshold. The reliable detection range of this vibrometer was less than 100×10^{-2}G. Any higher values than 100×10^{-2}G were considered as 100×10^{-2}G. The values at the end of each period were adopted as the vibratory threshold of the respective periods in each patient.

As an indicator of glycemic control, we determined glycosylated hemoglobin (HbA1c) every month from 3 months before the study (observation period). The means of HbA1c during the observation, the treatment and the washout periods were adopted as HbA1c values of the respective periods in each patient.

Statistical analysis: The data are presented as the mean ± SEM. Effects of epalrestat on subjective symptoms were evaluated by chi-square analysis, while its effect on vibratory threshold was evaluated by paired t-test. Changes in

HbA1c were evaluated by paired t-test. A level of $p<0.05$ was considered statistically significant.

Results

As we previously reported, the mean vibratory threshold in the lower extremity in the nondiabetic subjects rose gradually with the ages, being $16.5\pm8.5\times10^{-2}$G in the seventies, and the coefficient of variation of the measurement was 18.5%[12]. The normal values for the lower extremities were slightly, but not significantly higher than for the upper extremities in each decade, in agreement with the report of Suzuki[15].

Background: Table 1 shows the background characteristics of the patients studied. Glycemic controls were done by only dietary regimen in 4 patients, by oral hypoglycemic agents in 6 patients and by insulin in 9 patients. The cases with asterisks in HbA1c columns are those in whom HbA1c shifted more than 1% to the same direction with the vibratory threshold after the treatment or the washout period.

Effect of epalrestat on HbA1c: As shown in Fig. 1, there was no significant difference in mean HbA1c values as a whole by paired t-test throughout the study period.

Effect of epalrestat on subjective symptoms: Table 2 shows the effects of epalrestat on subjective symptoms. Epalrestat relieved numbness in 12 of 16 patients and other symptoms such as pain, paresthesia or cold sensation in 6 of 10 patients. After the washout period, numbness worsened in 5 of 11 patients and other symptoms worsened in 4 of 7 patients. Chi-square analysis revealed significant effects on numbness ($p<0.001$) and on other symptoms ($p<0.05$). Readministration of epalrestat after the washout period ameliorated numbness once again in 6 of 9 patients (data not shown).

Effect of epalrestat on vibratory threshold: Fig. 2 shows the changes in vibratory threshold after the

Table 1. Background characteristics

Case	Age	Sex	Duration of DM	Retinopathy	Nephropathy	Treatment	Treatment period		Washout period	
							$\triangle HbA_{1C}$ (%)	△VT	$\triangle HbA_{1C}$ (%)	△VT
HE	49	F	12	Simple	Mic	Ins	−0.3	0/−50	+0.6	+5/+40
II	57	M	6	Simple	—	Diet	+1.0	−4/0	+0.2	+7/0
FS	73	F	19	Proliferative	—	Ins	−0.2	−25/−15	−1.05*	0/−25
NF	59	M	8	Simple	Overt	Ins	−0.4	−13/0	+0.1	+18/0
KR	59	F	11	—	—	OHA	−0.8	−5/0	−0.1	+18/0
KY	43	M	12	—	—	OHA	−0.2	0/0	−0.1	0/0
OT	79	F	22	Simple	—	Ins	−2.7*	0/−35	+1.2*	+40/+35
KH	51	M	7	Simple	—	Ins	+0.2	−36/0		
NS	55	F	12	Simple	—	Ins	+1.1	−30/−40		
YM	67	F	6	Simple	—	Diet	+0.2	−18/−60	−0.1	+4/+50
NT	60	F	5	—	Mic	OHA	−0.1	+10/−20		
GM	73	F	13	Simple	Mic	OHA	−0.2	−24/−20	+0.1	0/0
AT	66	F	10	Simple	Overt	Ins	+0.6	+8/+2	0	+22/+20
HY	72	M	21	—	Mic	OHA	−0.3	+16/−32	+0.4	−14/+12
FY	70	M	13	—	Mic	Ins	−0.1	0/0	−0.1	0/0
TH	56	M	21	Simple	Mic	Ins	−1.2*	−30/0	−0.5	0/+28
IM	74	F	30	Proliferative	Overt	OHA	−0.6	−8/−20		
KR	59	M	8	—	—	Diet	−0.3	/−70		
KS	59	F	10	Proliferative	Mic	Diet	−1.5*	−14/	+0.5	+35/

Mic: Microalbuminuira, Overt: Overt albuminuira, Ins: Insulin, OHA: Oral hypoglycemic agents, DM: Diabetes mellitus, $\triangle HbA_{1C}$: The difference of mean HbA_{1C} compared to that of the preceding period, △VT: The difference of vibratory threshold compared to that of the preceding period in upper extremity/lower extremity, *: The data whose $\triangle HbA_{1C}$ was more than 1%.

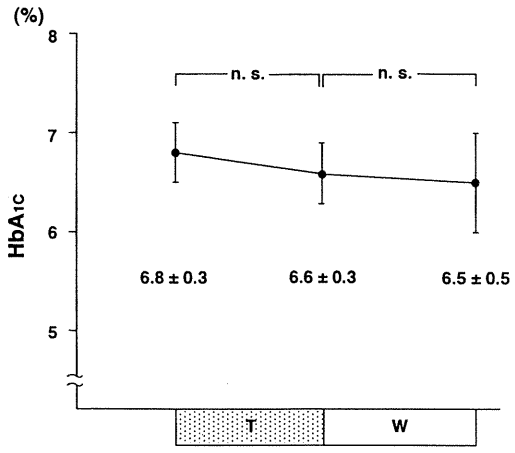

Fig. 1. Changes in mean HbA1c values after the treatment period (T) and the washout period (W).
The values are presented as the mean ± SEM. The statistical analyses were done by paired t-test. n.s.: not significant.

treatment and the washout periods. In this analysis, those with the asterisks in Table 1 had been excluded. The mean vibratory threshold both in the upper (Fig. 2 A) and the lower (Fig. 2 B) extremities decreased after the treatment period, and rose in the lower extremity after the washout period. There were significant changes by paired t-test in the upper extremity after the treatment period ($p < 0.05$) and in the lower extremity both after the treatment ($p < 0.01$) and the washout ($p < 0.05$) periods. Although not significant, the mean reduction in vibratory threshold of the lower extremity after the treatment period was greater in those who showed improvement of numbness (-22.9×10^{-2}G) than those without improvement (-9.5×10^{-2}G). Readministration of epalrestat again decreased mean vibratory threshold in the lower extremity (data not shown).

Discussion

So far, the measurement of nerve conduction velocity has been widely used as a standard method for assessing diabetic neuropathy[16]. However, Archer *et al.*[17] reported that nerve conduction velocity correlates poorly with the clinical findings. In addition, Greene *et al.*[18] also reported that nerve conduction velocity was not correlated with the amelioration of subjective symptoms in patients with diabetic neuropathy. These reports may indicate that measuring nerve conduction velocity is not always the best method to evaluate diabetic neuropathy, especially during the process of treatment. Recently, Goto *et al.*[9] reported the significant effect of epalrestat on motor nerve conduction velocity of the median nerve by double-blind study, whereas they did not observe significant effects on motor nerve conduction velocity of the peroneal nerve and sensory nerve conduction velocity of the median nerve. Although significant in their study, the difference in motor nerve conduction velocity of the median nerve between epalrestat and placebo

Table 2. Effect of epalrestat on subjective symptoms

		Epalrestat		P values
		Treatment period	Washout period	
Numbness	Improved	12	0	
	No change	4	6	<0.001
	Worsened	0	5	
Others	Improved	6	0	
	No change	3	3	<0.05
	Worsened	1	4	

Others include cold sensation, paresthesia and pain.
The data were analyzed by chi-square analysis.

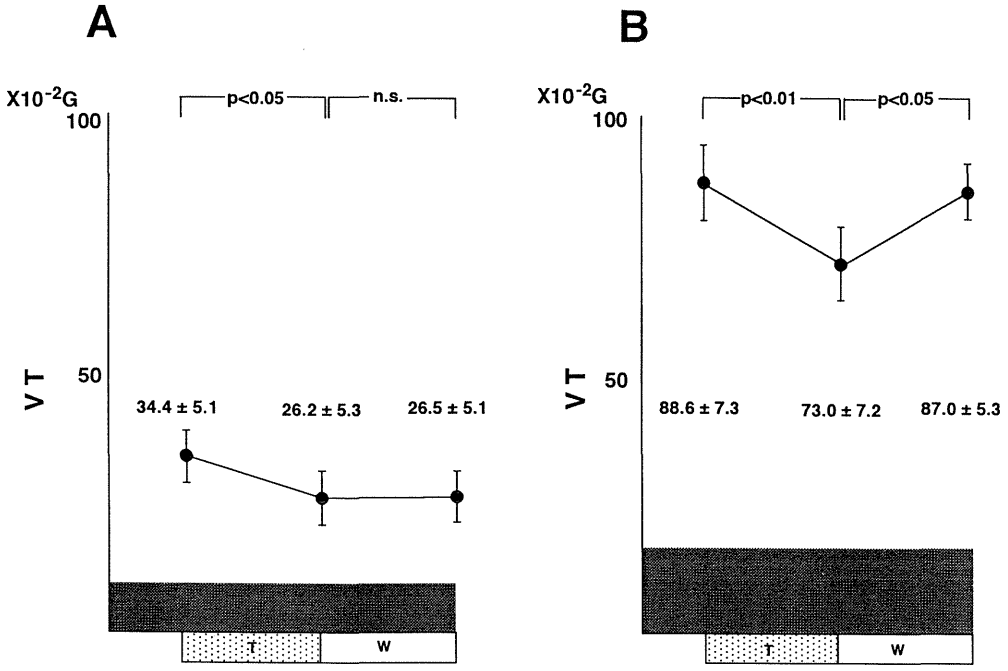

Fig. 2. Changes in vibratory threshold (VT) in the upper (A) and the lower (B) extremities after the treatment and the washout periods.
The values are presented as the mean ± SEM. The data with the asterisks in Table 1 were excluded from the statistical analyses. T and W indicate the treatment and the washout periods, respectively. The shaded areas represent the normal ranges for nondiabetic subjects in the seventh decade. There were significant differences by paired t-test in the upper extremity after the treatment period ($p < 0.05$) and in the lower extremity after the treatment ($p < 0.01$) and the washout ($p < 0.05$) periods.

is so small that we thought it is worthwhile to confirm the efficacy of epalrestat by another method. So, we evaluated the effect of epalrestat on vibration sensation by measuring vibratory threshold with SMV-5 vibrometer. Since impairment of vibratory sensation is one of the first signs of peripheral polyneuropathy in patients with diabetes mellitus[19], we think that the evaluation of epalrestat on vibratory sensation is relevant in diabetic neuropathy. Several instruments to evaluate vibration sensation have been developed to overcome the defects of tuning forks[10,11,20–23]. The coefficient variation of measuring vibratory threshold by these instruments ranged from 21%[21] to 12.85%[20]. In Japan, SMV-5 vibrometer is available[11], with the coefficient variation of 18.5%[12].

It is reported that vibratory threshold measured by SMV-5 vibrometer is improved by short term blood glucose control[10], and we also confirmed this in the previous study[13]. These data indicate that when we evaluate the efficacy of epalrestat on vibratory threshold, it is necessary to exclude the effect of HbA1c on vibratory threshold. So, statistical analyses were done by excluding the data of the patients whose HbA1c changed more than 1% as indicated with the asterisks in Table 1. We confirmed the efficacy of epalrestat on vibration sensation in patients with diabetic neuropathy as Goshajinkigan[14]. In addition, the effect of epalrestat on vibration sensation tended to be correlated with the effect on subjective symptom.

Goto *et al.*[9] did not observe the efficacy of epalrestat compared to placebo on nerve function tests in patients whose HbA1c leveles were less than 7%. And they discussed that the therapeutic value of epalrestat was likely to be depreciated in

cases with good diabetic control, i.e. with the HbA1c value<7%. In our study, mean HbA1c was 6.8%, and yet we observed the significant effect of epalrestat. Therefore, we think that measurement of vibratory threshold by SMV-5 vibrometer can be used for the assessment of a drug on diabetic neuropathy in patients even with relatively good glycemic control.

Mechanisms of action of aldose reductase inhibitor have been explained by its action on the inhibition of sorbitol synthesis and the increase in myoinositol, thereby increasing Na^+, K^+-ATPase activity in the peripheral nerve[7]. However, we have reported that cyclic AMP plays an important role in diabetic neuropathy[24–26], which was confirmed by Ohno *et al.*[27]. In addition, we have also reported that aldose reductase inhibitors such as epalrestat increase cyclic AMP in sciatic nerves of diabetic rats[24]. So, we think it is possible that aldose reductase inhibitors share a common pathway in its efficacy on diabetic neuropathy with agents which increase cyclic AMP in peripheral nerves such as iloprost[24,25,27] and cilostazol[25].

In conclusion, oral administration of epalrestat relieves subjective symptoms and improves vibratory sensation in patients with diabetic neuropathy without affecting glycemic control. Measuring vibratory threshold by SMV-5 vibrometer is a good parameter for the evaluation of drugs on diabetic neuropathy.

Acknowledgements

The authors are grateful to Mrs. Yukiko Sato, Miss Mayumi Orii and Miss Mari Shimegi for their assistance in the preparation of this manuscript.

References

1) Greene DA, Sima AAF, Pfeifer MA *et al.*: Diabetic neuropathy. Ann Rev Med, **41**: 303–317, 1990.
2) Dyck PJ, Hansen S, Karnes JL *et al.*: Capillary number and percentage closed in human diabetic sural nerve. Proc Natl Acad Sci USA, **82**: 2513–2517, 1985.
3) Dyck PJ, Lais A, Karnes JL *et al.*: Fiber loss is primary and multifocal in sural nerves in diabetic polyneuropathy. Ann Neurol, **19**: 425–439, 1986.
4) Johnson PC, Doll SC, Cromey DW: Pathogenesis of diabetic neuropathy. Ann Neurol, **19**: 450–457, 1986.
5) Young MJ, Veves A, Walker MG *et al.*: Correlations between nerve function and tissue oxygenation in diabetic patients : further clues to the aetiology of diabetic neuropathy. Diabetologia, **35**: 1146–1150, 1986.
6) Greene DA, Lattimer SA, Sima AAF: Perspectives in diabetes are disturbances of sorbitol, phosphoinositide, and Na^+, K^+-ATPase regulation involved in pathogenesis of diabetic neuropathy. Diabetes, **37**: 688–693, 1988.
7) Greene DA, Lattimer SA, Sima AAF: Pathogenesis and prevention of diabetic neuropathy. Diabetes Care, **4**: 201–221, 1988.
8) Greene DA, Lattimer SA: Action of sorbinil in diabetic peripheral nerve: relationship of polyol (sorbitol) pathway inhibition to a myo-inositol-mediated defect in sodium-potassium ATPase activity. Diabetes, **33**: 712–716, 1984.
9) Goto Y, Hotta N, Shigeta Y *et al.*: A placebo-controlled double-blind study of epalrestat (ONO-2235) in patients with diabetic neuropathy. Diabetic Med, **3** (Suppl. 2): 39S–43S, 1993.
10) Tomioka M, Kodama K, Ohtani T *et al.*: Suzuki-Matsuoka vibrometer (SMV-4) is easily swayed by short trem blood sugar control. Ann Jpn Soc Diab Complica, **3**: 65–71, 1990 (in Japanese with English abstract).
11) Suzuki Y, Matsuoka K: A process of inventing new vibratory sensation meter (SMV-5). Ther Res, **12**: 4189–4196, 1990 (in Japanese).
12) Shindo H, Tawata M, Inoue M *et al.*: The effect of prostaglandin $E_1 \cdot \alpha$CD on vibratory threshold determined with the SMV-5 vibrometer in patients with diabetic neuropathy. Diabetes Res Clin Pract, **24**: 173–180, 1994.
13) Tawata M, Nitta K, Kurihara A *et al.*: Effects of a single drip infusion of lipo-prostaglandin E_1 on vibratory threshold in patients with diabetic neuropathy. Prostaglandins, **49**: 27–39, 1995.
14) Tawata M, Kurihara A, Nitta K *et al.*: The effects of Goshajinkigan, a herbal medicine, on subjective symptoms and vibratory threshold in patients with diabetic neuropathy. Diabetes Res Clin Pract, **26**: 121–128, 1994.
15) Suzuki Y: A new instrument for the evaluation of diabetic neuropathy: vibrometer. Diabetes Frontier, **3**: 183–186, 1992 (in Japanese).
16) Report and recommendations of the San Antonio

conference on diabetic neuropathy. Neurology, **38**: 1161–1165, 1988.
17) Archer AG, Watkins PJ, Thomas PK *et al.*: The natural history of acute painful neuropathy in diabetes mellitus. J Neurol Neurosurg Psychiatry, **46**: 491–499, 1983.
18) Greene DA, Brown MJ, Brownstein SN *et al.*: Comparison of clinical course and sequential electrophysiological tests in diabetics with symptomatic polyneuropathy and its implications for clinical trials. Diabetes, **30**: 139–147, 1981.
19) Steines I: Vibratory perception in diabetes. A biothesiometric study. Acta Med Scand, **158**: 327–335, 1957.
20) Bertelsmann FW, Heimans JJ, van Rooy JCGM *et al.*: Reproducibility of vibratory perception threshold in patients with diabetic neuropathy. Diabetes Res, **3**: 463–466, 1986.
21) Krentz AJ, Honigsberger L, Nattrass M: Variability of three standard neurophysiological techniques in established symptomatic diabetic polyneuropathy. Diabetes Res, **12**: 135–139, 1989.
22) Armstrong FM, Bradbury JE, Ellis SH *et al.*: A study of peripheral diabetic neuropathy. The application of age-related reference values. Diabetic Med, **8**: S94–S99, 1991.
23) Maser RE, Nielsen VK, Bass EB *et al.*: Measuring diabetic neuropathy. Assessment and comparison of clinical examination and quantitative sensory testing. Diabetes Care, **12**: 270–275, 1989.
24) Shindo H, Tawata M, Aida K *et al.*: The role of cAMP and polyol metabolism in diabetic neuropathy. J Clin Endocrinol Metab, **74**: 393–398, 1992.
25) Shindo H, Tawata M, Onaya T: Cyclic adenosine 3', 5'-monophosphate enhances sodium, potassium - adenosine triphosphatase activity in the sciatic nerve of streptozotocin-induced diabetic rats. Endocrinology, **132**: 510–516, 1993.
26) Shindo H, Tawata M, Onaya T: Reduction of cyclic AMP in the sciatic nerve of streptozotocin-induced diabetic rats and the mechanism involved. J Endocrinol, **136**: 431–438, 1993.
27) Ohno A, Kanazawa A, Tanaka A *et al.*: Effect of a prostaglandin I2 derivative (Iloprost) on peripheral neuropathy of diabetic rats. Diabetes Res Clin Pract, **18**: 123–130, 1992.