

# Fidarestat Improved Symptoms of Diabetic Polyneuropathy

Vibration detection threshold was improved in patients enrolled in the 28-week study.

REVIEWED BY NIGISHI HOTTA, MD

**P**atients in an open-label study had improvement in vibration detection threshold (VDT) as well as in their symptoms of diabetic polyneuropathy with fidarestat.<sup>1</sup>

The aldose reductase inhibitor (ARI) was tested in 22 type 2 diabetic patients, aged  $\geq 20$  years, with polyneuropathy and stable blood glucose control (mean HbA1c 7.2%). Patients had not used another ARI  $\leq 3$  months before baseline. For 28 weeks, patients took 1mg of fidarestat, an investigational drug, daily before breakfast. Lead investigator Nigishi Hotta, MD, and colleagues were able to confirm results from previous studies that suggest that fidarestat (SNK-860, Sanwa Kagaku Kenkyusho, Nagoya, Japan) is an effective treatment for diabetic peripheral neuropathy.

Previously, Dr. Hotta studied the effects of fidarestat in 279 type 1 and type 2 diabetic patients with neu-

VDT had a negative correlation to upper and lower limb numbness, among other side effects.

ropathy during a double-blind placebo controlled study.<sup>2</sup> Patients in the previous study were treated with the same dose of the ARI as in the current study, however the duration of the trial was 52 weeks.

Investigators concluded that fidarestat altered the progression of diabetic neuropathy and positively affected subjective symptoms.

**POTENT, PROMISING ARI**

In an unrelated study,<sup>3</sup> investigators wrote that fidare-

**TABLE 1. CORRELATION BETWEEN VIBRATION DETECTION AND SUBJECTIVE SYMPTOMS AT BASELINE\***

Subjective nervous symptoms	Real (r)	P-value
<b>Upper extremity</b>		
• Numbness	-.6000	.0066
<b>Lower extremity</b>		
• Numbness	-.7307	.0004
• Coldness and hot flushes	-.5262	.0206
• Smarting pain, causing difficulty with walking	-.5845	.0086
• Hypoaesthesia of subjective senses	-.7125	.0006

\* Each correlation is calculated from parameters of the upper or lower extremity (n=19).

TABLE 2. VIBRATION DETECTION THRESHOLD

	Baseline	12 weeks	28 weeks
Upper extremity*	5.1 ±0.4	6.2 ±0.3	6.3 ±0.4
Lower extremity*	3.7 ±0.4	4.7 ±0.5	4.9 ±0.5

\*  $P=.0004$  (12 weeks) and  $P=.0002$  (28 weeks) versus baseline for upper extremity and  $P=.0014$  (12 weeks) and  $P<.0001$  (28 weeks) for lower extremity using a Bonferroni-type multiple comparison. Values represent mean ±standard error (n=18).

stat is a “potent and promising ARI, possibly useful for both preventing and treating diabetic neuropathy.” In that investigation, 58 type 2 diabetic patients took 1mg fidarestat daily for 4 weeks and experienced a normalization of elevated sorbitol content levels of erythrocytes.

Investigators of the current study, published in *Clinical Drug Investigation*, measured upper and lower extremity VDT and studied the severity of diabetic polyneuropathy symptoms with a C64 quantitative tuning fork (Takano Manufacturing Co, Nagoya, Japan) at baseline, 12 and 28 weeks. The upper extremity threshold test point was the third finger, and the lower extremity test point was the first toe. Both were done on the left extremities and were evaluated using the paired t-test.

Subjective symptoms were significantly improved in the lower extremity; improvements were not significant in the upper extremity.

Evaluation of VDT, which investigators concluded had a negative correlation to upper and lower limb numbness, cold and hot flushes, difficulty walking and hypoaesthesia, was performed in 19 patients (Table 1). Lower extremity threshold at baseline was  $3.6 \pm 0.4$  and  $4.8 \pm 0.5$  after therapy ( $P=.0001$ ). In the upper extremity, thresholds were  $4.9 \pm 0.4$  and  $6.3 \pm 0.4$ , respectively ( $P=.0017$ ) (Table 2).

### VDT EVALUATION

Patients with decreased VDT experienced numbness in their extremities that became worse as the threshold decreased, investigators noted. VDT of  $\leq 2$  denoted hypoaesthesia.

“These results suggest that development of hypoaes-

thesia indicates considerable neuropathic progress,” they wrote. “It is known that in diabetic polyneuropathy the sensory nervous system is disturbed, and vibration [detection] is reduced in the early stages of the disease process.”

Subjective symptoms were checked with the Friedman test once every four weeks: Paraesthesia, (numbness, rigidity, heaviness) spontaneous pain and hypoaesthesia (tactile sense, algaesthesia) were rated on a scale of 0 to 4, where 0 referred to no severity and 4 referred to severe.

### SUBJECTIVE SYMPTOMS IMPROVED

Results indicated that fidarestat significantly improved the subjective symptoms in the lower extremity including numbness, cold and hot flushes ( $P<.0001$ ), spontaneous pain ( $P=.0002$ ) and pain that caused difficulty walking ( $P=.0015$ ). Improvements in upper extremity were not statistically significant, the investigators wrote.

Diabetic polyneuropathy is usually present during early stages of diabetes. Polyol pathway acceleration, oxidative stress, accelerated glycation and abnormal protein kinase C metabolism may be the cause of the diabetes complication. Early treatment with fidarestat may prevent further complications from the dysfunction, investigators wrote. These may include myocardial infarction or sudden death. ■

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2. Hotta N, Toyota T, Matsuoka K, et al. Clinical Efficacy of Fidarestat, a Novel Aldose Reductase Inhibitor, for Diabetic Peripheral Neuropathy. *Diabetes Care.* 2001;24:1776-1782.
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