Aldose Reductase Inhibition by AS-3201 in Sural Nerve From Patients With Diabetic Sensorimotor Polyneuropathy

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OBJECTIVE — The primary purpose of this investigation was to determine whether AS-3201, a new aldose reductase inhibitor, penetrates the sural nerve and inhibits sorbitol and fructose accumulation in patients with diabetic sensorimotor polyneuropathy (DSP). An additional aim was to determine whether any changes in nerve function would manifest with AS-3201 therapy.

RESEARCH DESIGN AND METHODS — Patients with mild to moderate DSP based on nerve conduction studies were randomized into one of three treatment groups in a double-blind fashion: placebo or AS-3201 at 5 or 20 mg/day. After 12 weeks of administration, the sural nerve was biopsied for measurement of sorbitol, fructose, and AS-3201.

RESULTS — At baseline, no important clinical, electrophysiological, or laboratory differences were found between the three groups. The nerve sorbitol concentration of 3.14×10^{-2} nmol/mg wet nerve in patients in the placebo group was inhibited by 65 and 84% in patients on AS-3201 at 5 and 20 mg/day, respectively ($P < 0.001$). Fructose levels were similarly inhibited. Sensory nerve conduction velocities improved by ≥1 m/s ($P < 0.05$).

CONCLUSIONS — AS-3201 penetrates the sural nerve and inhibits sorbitol accumulation in patients with DSP. Additional studies are needed to confirm the electrophysiological suggestion that AS-3201 delays progression or leads to regression of DSP.

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Despite advances in the management of diabetes, diabetic sensorimotor polyneuropathy (DSP) continues to be a frequent and potentially serious complication leading to foot ulceration and amputation (1). A fundamental pathophysiologic mechanism in DSP is aberrant activity of the polyol pathway in which hyperglycemia increases aldose reductase enzyme activity (2). This activation in turn results in an increased conversion of glucose to sorbitol, leading to an accumulation of sorbitol and fructose in several organ systems, including erythrocytes, retina, kidneys, and various nerves. Laboratory studies in animals with diabetes have shown that increased nerve sorbitol is associated with nerve damage with decreased conduction velocity as a result of osmotic changes and oxidative stress (3). If the aldose reductase enzyme system could be pharmacologically inhibited with a decrease in nerve sorbitol and fructose levels, then nerve damage could be prevented or even possibly reversed.

A number of aldose reductase inhibitors (ARIs) have been developed, but none have achieved clinical success for diverse reasons (4,5). The study failures have provided information on the natural progression of DSP and have led to suggested criteria for clinical development of ARIs (5). In a recent trial, inhibition of nerve sorbitol levels was associated with improved motor nerve conduction velocity (NCV) and an increase in the density of small-diameter sural nerve myelinated fibers (6). These encouraging results support the role of the polyol pathway in the pathogenesis of DSP. Experience has shown that inhibition of human nerve sorbitol levels must be demonstrated for individual ARI agents to appropriately design efficacy trials because not all ARIs penetrate human peripheral nerve (7).

AS-3201, a novel ARI developed by Dainippon Pharmaceuticals (Osaka, Japan) demonstrates selective, reversible, and potent inhibition of the aldose reductase enzyme system. In diabetic rats, AS-3201 inhibits nerve sorbitol production in a dose-dependent fashion with an associated improvement in motor NCV when compared with both untreated diabetic animals and control animals. In humans, AS-3201 is well absorbed with a time to maximum plasma concentration (T_{max}) of 0.5–1.1 h, a distributive or α-phase half-life ($T_{1/2}$) of 1.3–5.0 h, and an excretory β-phase $T_{1/2}$ of 22–80 h.

We aimed to determine whether AS-3201 inhibits sorbitol and fructose accumulation in sural nerve from patients with DSP. Furthermore, we aimed to explore the functional changes in DSP that might predict future clinical benefit for patients treated with an ARI for a sufficient length of time.

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*A complete list of AS-3201 Study Group members can be found in the APPENDIX.

Abbreviations: ARI, aldose reductase inhibitor; DSP, diabetic sensorimotor polyneuropathy; NCS, nerve conduction study; NCV, nerve conduction velocity; TCNS, Toronto Clinical Neuropathy Score; VPT, vibration perception threshold

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

Table 1—*Patient demographic profile*

	Placebo	AS-3201 5 mg	AS-3201 20 mg	*P*
n	34	33	34	
Sex				
Male	20 (58.8)	24 (72.7)	22 (64.7)	0.487
Female	14 (41.2)	9 (27.3)	12 (35.3)	
Age (years)	58.1 ± 8.7	60.8 ± 7.6	56.9 ± 9.3	0.222
Race				
Caucasian	23 (67.6)	27 (81.8)	23 (67.6)	0.475
Hispanic	2 (5.9)	3 (9.1)	4 (11.8)	
African American	3 (8.8)	2 (6.1)	5 (14.7)	
Asian	3 (8.8)	1 (3.0)	1 (2.9)	
Other	3 (8.8)		1 (2.9)	
Weight (kg)	91.4 ± 15.5	92.7 ± 16.4	92.2 ± 21.0	0.866
Type of diabetes				
Type 1	2 (5.9)	3 (9.1)	5 (14.7)	
Type 2	32 (94.1)	30 (90.9)	29 (85.3)	0.468
Duration of diabetes (years)	15.4 ± 10.1	14.2 ± 8.8	14.7 ± 11.8	0.764
Duration of DSP (years)	4.4 ± 3.2	3.9 ± 3.3	3.9 ± 4.4	0.289
Fasting glucose level (mg/dl)	182.3 ± 69.2	169.1 ± 43.8	151.2 ± 62.2	0.455
Baseline HbA_{1c} (%)	8.49 ± 1.52	8.18 ± 1.18	8.43 ± 1.27	0.720

Data are *n* (%) or means ± SD. *P* values are based on the χ^2 test for sex, race, and type of diabetes and the Kruskal-Wallis test for mean age, weight, and other parameters.

RESEARCH DESIGN AND METHODS

— The trial was a multicenter, double-blind, randomized, placebo-controlled efficacy study in which patients were assigned to one of three treatment groups: AS-3201 5 mg/day; AS-3201 20 mg/day; or placebo for 12 weeks, an interval considered sufficient for AS-3201 to inhibit nerve sorbitol. The patients, technicians, research staff, and physicians were all masked to the treatment arm. The doses selected were those calculated to occupy 70% (5 mg/day AS-3201) and 89% (20 mg/day AS-3201) of the aldose receptor sites in a 70-kg person on the basis of the preclinical studies. The following procedures were performed at entry for each patient: medical history, physical and neurological examinations, nerve conduction studies (NCSs), vibration perception threshold (VPT) tests, and the Toronto Clinical Neuropathy Score (TCNS) (8). Clinical laboratory tests were performed for hematology, clinical chemistry, and urinalysis frequently during the 12-week study. Erythrocyte sorbitol and fructose levels as well as plasma AS-3201 concentration were also measured. At week 12, the entry procedures were all repeated and a sural nerve biopsy was performed for measurement of nerve sorbitol, fructose, and AS-3201. Patients were given the opportunity to enter an extension study in which all subjects received AS-3201.

Patients

We enrolled 101 patients who met the following criteria: 18–70 years of age, type 1 or 2 diabetes for at least 6 months, glycemic control stable for at least 3 months before entry, and HbA_{1c} ≥7.0% but ≤11.0%. DSP was diagnosed by the modified San Antonio Criteria, which required the presence of two of the following four criteria: *1*) symptoms of DSP, *2*) signs of DSP, *3*) abnormal results of NCS with at least two abnormal nerves, and *4*) abnormal results of VPT; presence of either of the latter two conditions was required (9). The requirement for sural nerve potential amplitude responses of at least 1.0 μV ensured the presence of sufficient nerve fibers to allow demonstration of sorbitol accumulation in peripheral nerves, if not inhibited by AS-3201. Patients with nondiabetic neuropathy or severe neuropathy (sural nerve amplitude <1.0 μV) or serum creatinine level >2.0 mg/dl were excluded. Patients with neuropathy related to uremia, toxins, nutritional deficiency, metabolic disorders, autoimmune disorders, genetic factors, and inflammatory demyelinating neuropathies were excluded based on medical history and laboratory findings. Patients with any clinically significant abnormal clinical laboratory parameter or any abnormal liver function test were excluded. The institutional review boards at each of the six participating centers reviewed and approved the study. All patients provided written informed consent at screening. Results of NCS and VPT and the entry criteria for each patient were reviewed and approved by the central core laboratory before a patient could be randomized. This central supervision ensured consistency of study procedures and high-quality data (10).

Study end points

The primary end point was the sorbitol inhibition in the sural nerve. Secondary end points were nerve fructose inhibition, penetration of AS-3201 into the sural nerve, sorbitol and fructose concentrations in erythrocytes, AS-3201 concentration in plasma, and the safety of AS-3201 in this patient population. NCS, VPT, and the TCNS were exploratory end points measured without any expectation of change due to the brief duration of the study.

Analytic procedures

Electrophysiologic measurements. A training meeting was held with all investigators to review the protocol and standard operating procedures. Each site was provided with a standard operating manual of the nerve conduction and reporting procedures. Each site was monitored by a clinical research organization, and, if necessary, the core laboratory performed site visits. Before randomizing patients in the study, each site completed measurements for two normal subjects twice to familiarize the sites with the protocol and the procedures.

Testing was standardized for temperature, side of testing, stimulation protocol, averaging sensory potentials, marking latencies and amplitudes, and providing information for the core laboratory. Before randomization of patients to active treatment, all NCSs had to be approved and accepted in the baseline interval.

Standardized techniques for NCS with temperature control and fixed distal distances were used. The minimum temperature was maintained at 32°C in the forearm and at 31°C in the lower calf using a surface thermal probe and heating

Table 2—*Baseline NCS, TCNS, and VPT results*

	Treatment group			
		AS-3201		
	Placebo	5 mg	20 mg	*P*
Sural				
Right				
Amplitude	5.0 ± 4.4	3.9 ± 2.4	4.9 ± 4.0	0.708
Velocity	42.5 ± 4.5	41.7 ± 5.1	40.2 ± 5.3	0.087
Left				
Amplitude	5.1 ± 4.4	3.9 ± 2.5	4.4 ± 2.8	0.831
Velocity	42.2 ± 4.1	41.7 ± 5.7	39.9 ± 4.5	0.083
Median sensory				
Proximal				
Amplitude	7.8 ± 4.6	7.3 ± 3.9	8.0 ± 5.1	0.806
Velocity	54.9 ± 5.1	55.4 ± 4.8	53.9 ± 4.6	0.203
Distal				
Amplitude	16.7 ± 11.3	16.3 ± 8.8	15.6 ± 9.9	0.922
Velocity	46.3 ± 10.5	49.1 ± 7.1	48.2 ± 6.0	0.662
Median motor				
Amplitude, wrist	8.9 ± 3.0	9.0 ± 2.6	9.6 ± 3.2	0.538
Velocity	50.0 ± 4.0	52.4 ± 3.4	49.7 ± 4.1	0.007*
Peroneal motor				
Amplitude, knee	3.8 ± 2.1	3.6 ± 1.7	4.1 ± 2.3	0.582
Velocity	39.8 ± 3.0	40.7 ± 3.3	38.9 ± 4.7	0.330
F-wave latency				
Median	30.4 ± 3.0	29.3 ± 2.7	30.2 ± 3.2	0.387
Peroneal	55.3 ± 6.6	54.6 ± 6.9	55.7 ± 7.3	0.769
VPT				
Right toe	20.3 ± 8.0	22.4 ± 9.3	21.2 ± 6.6	0.679
Left toe	20.9 ± 8.8	21.7 ± 9.6	20.5 ± 6.5	0.962
TCNS	10.4 ± 3.5	10.2 ± 3.0	9.9 ± 4.2	0.729

Data are means ± SD. All NCVs are m/s; sensory potential amplitudes are μV, motor potential amplitudes are mV, F-wave latencies are ms, VPT are V. *P* values are based on the Kruskal-Wallis test. *$P < 0.05$.

packs when necessary. At least 20 min of warming was used to allow equilibration between internal structures and surface skin temperatures. Unilateral NCSs were performed on the nondominant median motor, dominant peroneal motor, and nondominant median sensory nerves. Bilateral sural sensory NCS were performed. Sensory NCS were performed antidromically. All stimulation and recording were performed using surface electrodes. The fixed distal distances for motor NCS were 70 mm for the median nerve and 90 mm for the peroneal nerve. Corresponding distances for sensory NCS were 20 mm proximal to the distal wrist crease for the median nerve and 140 mm for the sural nerve. Measurements of distances, response latencies, and amplitudes were performed in a standard fashion using onset latencies and baseline-to-peak amplitudes. Measurements from the initial positive peak to negative peak were made for sensory responses. F waves were generated for all motor nerves with 10 supramaximal stimuli per nerve, and the minimal reproducible latency of at least three responses was measured. Conduction velocities were calculated for motor and sensory nerves. All tracings from NCS and case report forms were reviewed by the core laboratory for quality control, and approval of the NCS was required before randomization of the subject at entry and before sural nerve biopsy at the end of 12 weeks of treatment.

Nerve biopsy collection. A 4-cm section of the sural nerve was surgically removed under local anesthesia, divided into three segments, and immediately frozen to −70°C using liquid nitrogen. A 2-cm segment was used for sorbitol and fructose assays, a 1-cm segment was used for AS-3201 assay, and the third segment was held in reserve for additional studies, if necessary.

Biochemical measurements. Tandem Laboratories (Salt Lake City, UT) performed the following assays and sural nerve and plasma AS-3201 assays, sural nerve and erythrocyte sorbitol and fructose. Samples for the AS-3201 assay were prepared by a solid-phase extraction procedure, samples for the sorbitol and fructose assay were prepared by protein-precipitation followed by a solid-phase extraction procedure, and both samples were analyzed by liquid chromatography/tandem mass spectrometry. Because endogenous sorbitol and fructose are present in human nerve and erythrocytes, labeled sorbitol (Sorbitol-^{13}C6) and fructose (Fructosel-^{13}C6) standard curves and quality control statistics were used in extraction evaluation and quantitation. For nerve and plasma AS-3201 assays, calibration standards were prepared by spiking blank, homogenized human nerve tissue or plasma with the appropriate spiking solutions provided by Dainippon Pharmaceuticals (Osaka, Japan). The API 4000 was operated in the selected-reaction monitoring mode under optimized conditions for the detection of sorbitol or fructose negative ions formed by atmospheric pressure chemical ionization, and the API 3000 was operated in the selected-reaction monitoring mode under optimized conditions for detection of AS-3201 negative ions formed by TurboIonSpray ionization (11).

VPT

VPT was measured at the first toe by the method of limits using a Neurothesiometer (Horwell Scientific, London, U.K).

Statistical analyses

Demographic and baseline characteristics were analyzed for homogeneity using the Kruskal-Wallis or χ^2 test. An intention-to-treat analysis was performed. Within-group comparisons between the baseline value and postdose value were assessed using the Student's paired *t* test. ANCOVA was constructed to test for effects of treatment. Comparisons of groups were assessed using an ANCOVA model including baseline values as covariates. Medically meaningful predefined covariates were not included in the model if they were found to be homogeneous at baseline.

Table 3—*Sural nerve sorbitol, fructose, and nerve AS-3201 levels*

	Treatment group		
		AS-3201	
	Placebo	5 mg	20 mg
n	33	31	29
Sorbitol concentration (nmol × 10^{-2}/mg wet nerve)	3.14 ± 3.58	1.09 ± 0.65*	0.52 ± 0.21*†
Reduction rate (%)	NA	65.2	83.5
Fructose concentration (nmol × 10^{-2}/mg wet nerve)	18.69 ± 13.66	10.38 ± 6.72*	6.00 ± 3.65*‡
Reduction rate (%)	NA	44.4	67.9
AS-3201 concentration (ng/g wet nerve)	NA	108.37 ± 44.022	258.09 ± 108.113

Data are means ± SD. *Different from placebo, $P < 0.001$ based on ANCOVA; †different from 5-mg dose, $P < 0.001$ based on ANCOVA; ‡different from 5-mg dose, $P = 0.003$ based on ANCOVA. NA, not applicable.

RESULTS — A total of 295 patients were screened; 101 patients fulfilling the entry criteria were randomized. The entry demographic characteristics are displayed by treatment group in Table 1. A total of 33 patients were randomized to AS-3201 5 mg/day, 34 patients were randomized to AS-3201 20 mg/day, and 34 patients were randomized to placebo. A total of 94 of the 101 patients randomized to study medication completed the 12-week treatment interval and underwent the scheduled nerve biopsy. The demographic characteristics were similar for all three groups; there were no statistically significant differences (Table 1). Table 1 also summarizes details of the diabetes history of these patients. Most patients had type 2 diabetes, as expected in most North American clinics. The patients had diabetes for ~15 years and DSP for ~5 years before entering the study. HbA_{1c} and duration of DSP were similar for the three groups. Baseline NCS, TCNS, and VPT data are presented in Table 2. The mean NCS results show that the three treatment groups are similar at baseline; only one statistically significant difference existed in the median nerve motor conduction velocity, which likely occurred by chance alone. DSP was mild to moderate in severity, based on the NCS and TCNS results.

Of the 101 randomized patients, biopsy specimens were available for analysis in 33 of 34 patients in the placebo group, 31 patients in the group randomized to AS-3201 5 mg/day, and 29 patients randomized to AS-3201 20 mg/day. Six of the patients assigned to AS-3201 treatment elected to withdraw for diverse reasons unrelated to the study medication. Technical factors were implicated in missing biopsy data from two other patients (one from the placebo group and one assigned to AS-3201 5 mg/day). The mean nerve sorbitol and AS-3201 levels, as measured in the 93 sural nerve samples, are displayed in Table 3. Those who received the placebo had a mean nerve sorbitol concentration of 3.14 × 10^{-2} nmol/mg wet nerve. The mean nerve sorbitol concentration in the group who received AS-3201 5 mg/day was 1.09 × 10^{-2} nmol/mg wet nerve, a 65.2% reduction compared with the placebo group (Fig. 1). For those who received AS-3201 20 mg/day, the mean nerve sorbitol concentration was 0.52 × 10^{-2} nmol/mg wet nerve, an 83.5% reduction compared with the placebo group. The nerve sorbitol concentration in both AS-3201 groups was significantly lower than that found in

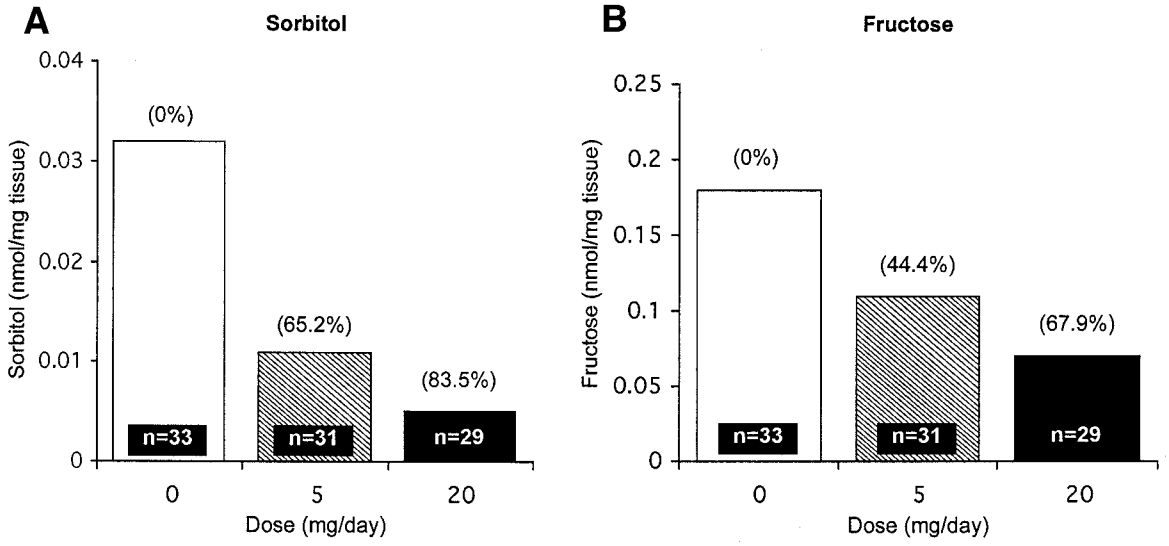

Figure 1—*Reduction in sural nerve polyol levels compared with placebo levels expressed as the percentage of reduction in the concentration.* A: *Reduction in sorbitol levels compared with placebo.* B: *Reduction in fructose levels compared with placebo.*

Table 4—*Plasma concentrations of AS-3201 (ng/ml)*

	Treatment group		
		AS-3201	
	Placebo	5 mg	20 mg
Week 2	ND	209.84 ± 55.87	661.41 ± 265.79
Week 4	ND	218.44 ± 71.25	671.86 ± 323.79
Final visit	ND	213.94 ± 66.28	717.99 ± 372.12

Data are means ± SD. ND, not detectable (<2 ng/ml).

the placebo group ($P < 0.001$) and significantly different between the AS-3201 groups ($P < 0.001$). Sural nerve fructose inhibition was similar to the sorbitol level inhibition: 44.4% inhibition compared with placebo for patients treated with AS-3201 5 mg/day and 67.9% for patients treated with 20 mg/day as shown in Table 3 and Fig. 1.

The mean sural nerve AS-3201 concentration in the 5-mg/day treatment group of 108.37 ng/g wet nerve and in the 20-mg/day group of 258.09 ng/g wet nerve shows a dose-dependent penetration of sural nerve and indicates overall patient compliance. No nerve AS-3201 was detected in the placebo control group, showing that the assay is specific for AS-3201.

Table 4 shows the plasma AS-3201 levels at different time points during the study. None was detected in the placebo group. After 2 weeks of administration, the mean level was 209.84 ng/ml in the 5-mg/day group and 661.41 ng/ml in the 20-mg/day group; only a small change was noted at week 4 and the final visit. Erythrocyte sorbitol and fructose levels were measured at baseline, week 4, and the final visit. These levels did not demonstrate a dose-response or correlation with nerve sorbitol levels.

Table 5 shows the changes from baseline in NCS parameters after 12 weeks of treatment. Placebo patients showed either slight deterioration in NCV or no change (Fig. 2). Patients randomized to AS-3201 5 mg/day were similar to the placebo group. However, those patients who received 20 mg/day demonstrated improvement in NCV of the right and left sural and proximal median sensory nerves and the median motor F-wave latency, which achieved statistical significance.

VPT did not change with 12 weeks of AS-3201 treatment. The total TCNS did not change, but subsections did improve (the signs improved).

AS-3201 was well tolerated for 3 months of administration. The prevalence of treatment-emergent adverse events was similar in the three groups: 79% in placebo, 70% in AS-3201 5 mg/day, and 71% in AS-3201 20 mg/day. No significant changes in renal or liver function were observed with treatment.

CONCLUSIONS — This biopsy study confirms the pathophysiological significance of the polyol pathway in DSP by demonstrating *1*) that AS-3201 decreases nerve sorbitol and fructose concentration and *2*) that inhibition of the elevated polyol levels in patients with DSP by ARI treatment is associated with functional improvement in sensory nerve activity. The placebo patients had sorbitol accumulation consistent with reports from other studies in which the nerve sorbitol levels ranged from 0.05 to 0.300 nmol/mg wet nerve in patients with DSP (12). Because glycemic control, represented as HbA_{1c}, was the same across the treatment groups, the differences in nerve sorbitol levels are an indication of an independent drug effect.

Consistent with preclinical radioautographic studies, the results of the current study show excellent dose-dependent AS-3201 human nerve penetration. Both doses used in this study demonstrate pharmacodynamic inhibition of nerve sorbitol. The different degrees of inhibition by AS-3201, such that 5 mg/day for 3 months inhibited sural nerve sorbitol levels by 65.2% and fructose levels by 44.4% and the higher dose of 20 mg/day inhibited nerve sorbitol levels by 83.5% and fructose production by 67.9%, predict that 5 mg/day AS-3201 is likely to be a suboptimal and ineffective clinical dose. Doses of ≥20 mg/day are predicted to be the appropriate clinical doses for the management of DSP. AS-3201 plasma levels remained steady from week 2 through the end of the study as anticipated from the β-phase half-life of 22–80 h. The plasma levels are relatively proportional to dose with no evidence of zero order or nonlinear kinetics. The lack of correlations between erythrocyte and nerve sorbitol levels prevents the use of erythrocyte sorbitol measurements as surrogate markers for nerve sorbitol, as has been found in previous ARI studies.

The reduction of nerve sorbitol achieved by the 20-mg/day group demonstrates the potency of AS-3201. In previous studies, a zenarestat dose of 1,200 mg/day was necessary to achieve a similar reduction (6).

This study has demonstrated that AS-3201 is well tolerated for 12 weeks of administration up to 20 mg/day based on the side effect profile, clinical examinations, and various laboratory safety stud-

Table 5—*Changes in NCV and F-wave latency from baseline*

	Treatment group			
		AS-3201		*P* (20-mg group)
	Placebo	5 mg	20 mg	
NCV (m/s)				
Sural, right	−0.11 ± 2.77	0.14 ± 2.50	1.36 ± 3.60	0.035*
Sural, left	−0.21 ± 3.43	−0.48 ± 2.32	1.26 ± 3.52	0.045*
Median sensory, proximal	0.10 ± 3.87	0.25 ± 3.26	1.95 ± 3.81	0.007*
Median sensory, distal	0.20 ± 3.23	0.52 ± 2.75	0.51 ± 2.74	0.300
Median motor	−0.39 ± 3.62	−0.07 ± 2.17	0.20 ± 3.04	0.704
Peroneal motor	−0.44 ± 2.06	0.25 ± 2.10	0.18 ± 1.72	0.540
F-wave latency (ms)				
Median, wrist	−0.05 ± 1.65	−0.10 ± 1.31	−0.57 ± 1.31	0.017*
Peroneal, ankle	−0.27 ± 3.25	−0.03 ± 3.61	−0.35 ± 2.14	0.424

Data are means ± SD. *P* values are the results of the Student's paired *t* test within 20-mg/day group comparison between baseline and the final visit values. *$P < 0.05$

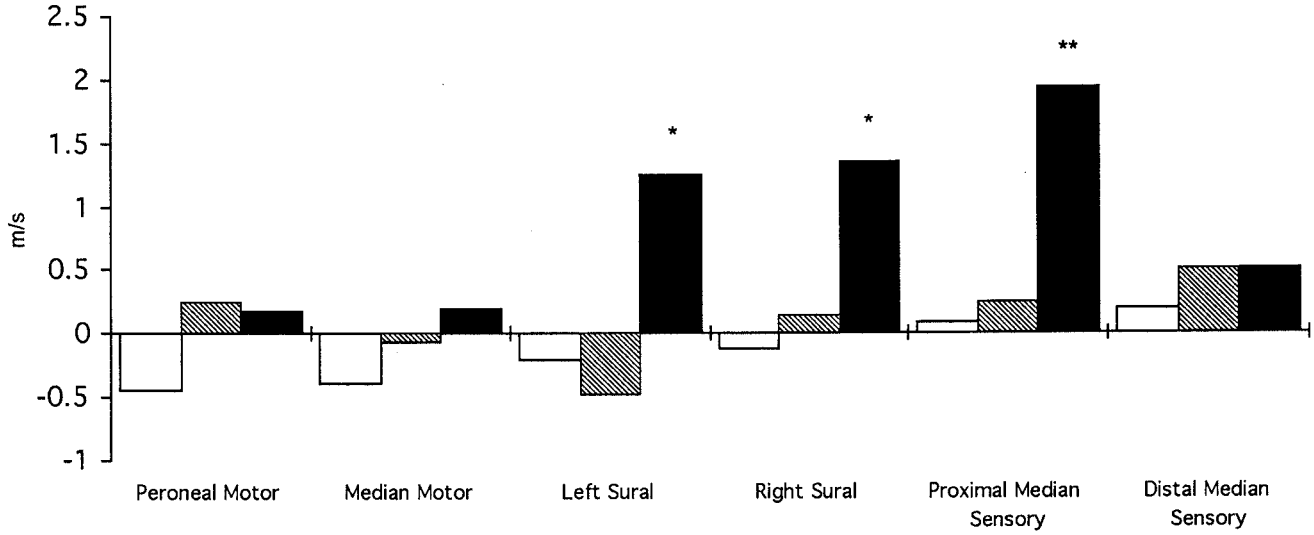

Figure 2—*Changes in NCV during the 12-week study for the placebo (□), AS-3201 5 mg/day (▨), and AS-3201 20 mg/day (■) groups. The proximal median sensory NCV and both sural NCVs showed a significant change of ≥1 m/s after 12 weeks of treatment with AS-3201 20 mg/day (*P < 0.05). **P < 0.01.*

ies. Particularly encouraging is the absence of renal or liver abnormalities with AS-3201 treatment in this study.

In addition to the biochemical outcomes of this study, promising functional and clinical changes were discovered. The minimal sensory NCV improvement found in the patients who received AS-3201 5 mg/day with a nerve sorbitol level inhibition of 65.2% means that this dose will likely prove to be less clinically effective; much longer treatment durations may be necessary to observe any clinical benefits in DSP at this dose. However, the improved sensory NCV observed in the group who received 20 mg/day for 3 months combined with an 83.5% inhibition of nerve sorbitol levels indicates that 20 mg/day is more likely to be an effective dose. The correlation observed between the inhibition rate of 83.5% and improvement in sensory NCV supports the polyol pathway as a possible pathogenic mechanism for DSP. These changes in NCS results were unexpected after 3 months of treatment because several authors have suggested that at least 1 year of ARI administration is required to detect any difference in NCV when compared with a placebo group (5,7). Others have stated that efficacy of an ARI is based on preventing deterioration of nerve function rather than specific functional improvement (13). In contrast, the results of the current study show a significant improvement in sensory nerve function after 12 weeks of treatment with an ARI. The NCV improvement in both sural nerves and in the proximal median sensory nerve exceeded 1 m/s, a level suggested by the Diabetes Control and Complications Trial results to be clinically significant, taking study duration into consideration (14). Therefore, the current results show promise for AS-3201 to be a clinically significant treatment for DSP.

Although the role of the polyol pathway in DSP is well accepted, this study provides the proof-of-concept for a specific ARI agent in achieving effective inhibition of the pathway. Furthermore, it provides preliminary efficacy data that warrants additional study with AS-3201.

APPENDIX

AS-3201 Study Group

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