

Drug for Diabetic Nerve Damage Shows Promise

A new aldose reductase inhibitor may be a potential treatment for diabetic sensorimotor polyneuropathy.

REVIEWED BY VERA BRIL, MD

A new aldose reductase inhibitor, AS-3201, penetrates the sural nerve and inhibits sorbitol accumulation in patients with diabetic sensorimotor polyneuropathy (DSP), according to researchers from the University of Toronto. "Additional studies are needed to confirm the electrophysiological suggestion that AS-3201 delays progression or leads to regression of DSP," said Vera Bril, MD, and colleagues in a report in *Diabetes Care*.¹

The investigators said that despite advances in the management of diabetes, DSP continues to be a frequent complication leading to foot ulceration and amputation. "A fundamental pathophysiologic mechanism in DSP is aberrant activity of the polyol pathway in

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which hyperglycemia increases aldose reductase enzyme activity," Dr. Bril said. The activation leads to an increased conversion of glucose to sorbitol and fructose. Studies have indicated that increased sorbitol in the nerves of animals is associated with damage.^{2,3} The investigators of this current study hypothesized that if the aldose reductase enzyme system could be inhibited

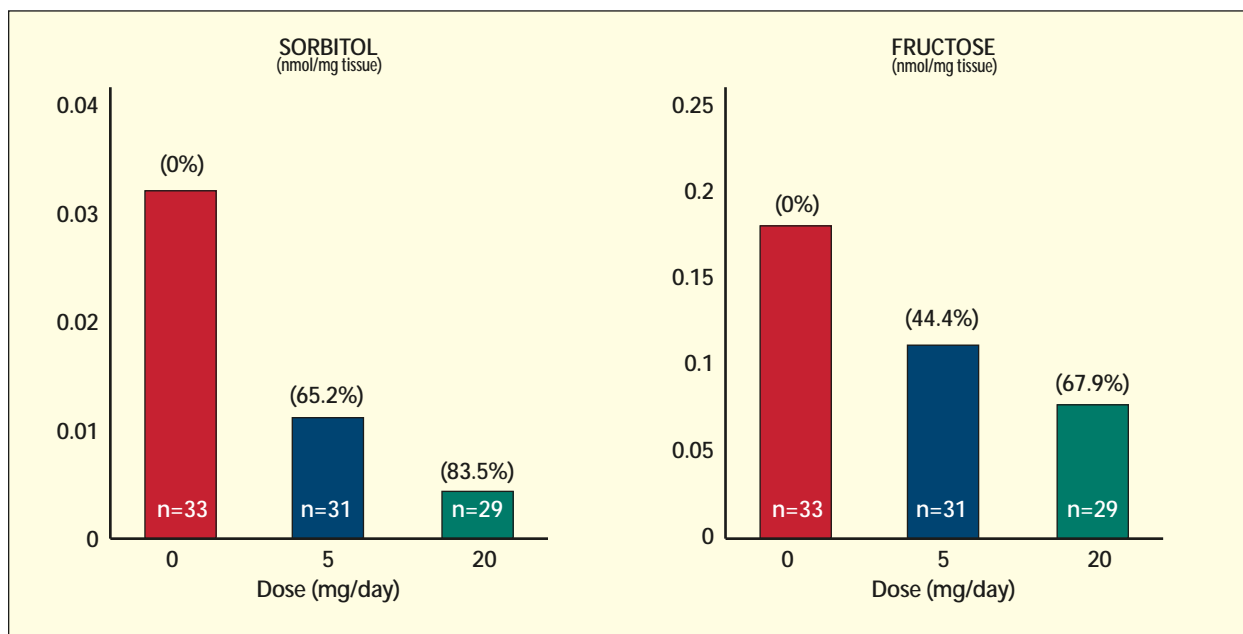


Figure 1. A reduction in sural nerve polyol levels versus placebo levels is expressed as the percentage of reduction in the concentration. The left graph shows a reduction in sorbitol levels compared with placebo. The right shows reduction in fructose levels compared with placebo. (Courtesy of *Diabetes Care*, American Diabetes Association.)

TABLE 1. MODIFIED SAN ANTONIO CRITERIA

The presence of two of the following four criteria are required:

1. symptoms of DSP
2. signs of DSP
3. abnormal results of NCS with at least two abnormal nerves
4. abnormal results of VDT
(presence of either of the latter 2 conditions was required)

pharmacologically, the consequences could be prevented or possibly reversed.

POTENT INHIBITION

The novel aldose reductase inhibitor (ARI) used in this study was developed by Dainippon Pharmaceuticals, and demonstrates selective, reversible and potent inhibition of the aldose reductase enzyme system. "We aimed to determine whether AS-3201 inhibits sorbitol and fructose accumulation in sural nerve from patients with DSP," Dr. Bril wrote. "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."

Patients in the multicenter, double-blind, randomized, placebo-controlled efficacy study were assigned to one of three treatment groups: AS-3201 5 mg/day, AS-3201 20 mg/day or placebo for 12 weeks. Upon patient entry, a medical history, physical and neurological examinations, nerve conduction studies, vibration detection threshold tests and the Toronto Clinical Neuropathy Score were performed. Patients also had clinical laboratory tests.

SUFFICIENT NERVE FIBERS

The 101 patients enrolled had type 1 or type 2 diabetes for at least 6 months, were 18 to 70 years old, had stable glycemic control for at least 3 months prior to entry and HbA1c $\geq 7\%$ but $\leq 11\%$. DSP was determined by modified San Antonio Criteria, according to Dr. Bril (Table 1). "The requirement for sural nerve potential amplitude responses of at least 1 μV ensured the presence of sufficient nerve fibers to allow demonstration of sorbitol accumulation in peripheral nerves, if not inhibited by AS-3201.

The investigators determined a study endpoint of sor-

bitol inhibition in the sural nerve. Secondary endpoints 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 compound's safety.

Dr. Bril and colleagues reported that there were no significant clinical, electrophysiological or laboratory baseline differences between the 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 assigned AS-3201 at 5 mg/day and 20 mg/day, respectively ($P < .001$). The levels of fructose were similarly inhibited, they reported, and sensory nerve conduction velocities (NCV) improved by ≥ 1 m/s ($P < .05$) (Figure 1).

PROMISING OUTCOMES AND CHANGES

Biochemical outcomes as well as functional and clinical changes in this study were promising, Dr. Bril wrote. "The improved sensory NCV observed in the group who received 20 mg/day for 3 months combined with an 83.5% inhibition of the nerve sorbitol levels indicates that 20 mg/day is more likely to be an effective dose," she wrote. "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."

The improved outcomes after just 3 months were unexpected, as earlier data suggested at least 1 year of treatment would be needed.

She added that the results were unexpected after just 3 months, as previous authors suggested at least 1 year of treatment was required to detect any changes. While the role of the pathway is well established, this study provides proof of concept for a specific ARI agent and warrants additional study, the authors concluded. ■

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