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Permalink

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Journal

JAMA, 311(16)

ISSN

0098-7484

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Publication Date

2014-04-23

DOI

10.1001/jama.2014.3325

Peer reviewed

Acetazolamide for Pseudotumor Cerebri Evidence From the NORDIC Trial

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After sulfanilamide was introduced as an antibiotic it was found to inhibit carbonic anhydrase, but too weakly to be a useful diuretic for patients with congestive heart failure.¹ In search of a



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more potent compound, Roblin and Clapp synthesized 20 heterocyclic sulfonamides and discovered $C_4H_6N_4O_3S_2$, an agent with 2000 times the inhibitory activity of sulfanilamide.² Named acetazolamide, it was soon tested for its ability to lower intracranial pressure. Maren and colleagues administered the drug to 20 institutionalized children with hydrocephalus.³ Mean spinal pressure declined from 237 mm H_2O at baseline to 128 mm H_2O with a low dose (19 mg/kg/d) and 68 mm H_2O with a high dose (61 mg/kg/d). Acetazolamide subsequently became accepted as a treatment for patients with high intracranial pressure. However, there has never been a randomized clinical trial to prove that it is effective.⁴

In this issue of *JAMA* the Neuro-Ophthalmology Research Disease Investigator Consortium (NORDIC)⁵ provides the evidence that has been lacking. Patients with pseudotumor cerebri (also termed *idiopathic intracranial hypertension*) were assigned randomly to 2 groups: 86 received acetazolamide and 79 received placebo. The primary outcome was function in the worst eye, measured by a Humphrey 24° visual field examination 6 months after enrollment. The Humphrey instrument provides a sensitive, reproducible, and quantitative measurement of retinal sensitivity at 54 points in the central visual field. The results are summarized by a single number: the perimetric mean deviation (PMD), which corresponds to the average decrease in retinal sensitivity at the tested points. In healthy adults the PMD is centered around zero. The scale is logarithmic, so a PMD of -10.0 dB corresponds to a serious, 10-fold loss of retinal sensitivity.

At baseline, PMD was -3.53 dB in both groups. At 6 months, PMD was -2.10 dB in the acetazolamide group and -2.82 dB in the placebo group. The difference was less than 1 dB. Although the findings were statistically significant ($P = .05$), the improvement was subtle, less than the 1.3 dB treatment effect predicted by a pilot study. Mindful that more was expected, the authors caution that “the clinical importance of this improvement remains to be determined.”

The study design posed a dilemma. Only patients with mild vision loss could be enrolled, because treatment with a placebo could not be justified in individuals with more serious vision loss. However, patients with mild vision loss have little room to improve and therefore any treatment effect will be modest. Having enrolled only patients with mild disease, it was

impressive that the NORDIC investigators still managed to uncover evidence for a statistically significant benefit from acetazolamide treatment. The clinical importance of the NORDIC trial will be greatest for patients with severe papilledema, who stand to gain the most from the drug. That conclusion was supported by the study’s finding that the treatment effect was 2.27 dB in 90 patients with more advanced papilledema (grades 3-5) compared with -0.67 dB in 75 patients with mild papilledema (grades 1-2). Patients with pseudotumor cerebri who have only a few decibels of visual field loss should not necessarily be treated with acetazolamide. The adverse effects of the drug may outweigh the slight improvement in visual function.

Why wasn’t reduction of intracranial pressure chosen to be the primary outcome measure? If the NORDIC trial had tested a drug that lowered arterial pressure, rather than intracranial pressure, the most appropriate outcome measure would have been blood pressure. The reason is that measurement of intracranial pressure requires an uncomfortable, invasive procedure. Performing a lumbar puncture in a patient with pseudotumor cerebri is often difficult and erroneous readings are not uncommon. Even if the opening pressure is recorded accurately, it represents only a single value for a parameter that varies substantially during the course of a normal day. There is an urgent need for a reliable, noninvasive technique to measure human intracranial pressure. Until then, clinicians must rely on examination of the optic fundi for the presence of papilledema. In the NORDIC trial there was a clear treatment effect ($P < .001$) on the severity of papilledema, providing further proof that acetazolamide is beneficial. There was also a 62% (117/72 mm H_2O) greater decline in intracranial pressure with acetazolamide compared with placebo, but the result did not achieve statistical significance ($P = .08$), probably because half the patients refused (quite understandably) to have a follow-up lumbar puncture at 6 months.

The dose of acetazolamide in this study was higher than used by most clinicians. Most patients are prescribed 2 or 3 500-mg acetazolamide extended-release capsules a day. In the NORDIC trial, patients were treated with 1 g twice daily, increasing the dose as needed to an upper limit of 2 g twice daily. The mean dosage was 2.5 g/d, an amount that will not be tolerated well by many patients. Not surprisingly, reports of paresthesia, nausea, vomiting, dysgeusia, and diarrhea were common. Acetazolamide can cause electrolyte disturbances, metabolic acidosis, abnormal liver enzyme levels, and kidney stones. If patients are treated at doses higher than 1 g/d, their medical condition should be monitored carefully.

The main benefit of acetazolamide is achieved by inhibition of carbonic anhydrase in the choroid plexus, but it also may have worked in the NORDIC trial by causing loss of appetite. Patients treated with acetazolamide lost a mean of 7.5 kg, twice the amount lost by control participants. Obese patients can reach a tipping point, whereupon a small additional weight gain can push intracranial pressure into the danger zone. Patients with new-onset papilledema often report a history of recent weight gain. Losing just 6% of body weight can lead to marked reduction in papilledema.⁶ All patients in the NORDIC trial were counseled regarding weight loss, which unavoidably may have attenuated the treatment effect of acetazolamide. Weight loss is so helpful as a treatment for pseudotumor cerebri that some authors have suggested that bariatric surgery should be considered for patients who do not respond to dietary measures.^{7,8}

The obesity epidemic has increased the prevalence of pseudotumor cerebri.⁹ Consequently, the health care costs associated with the treatment of this disease have escalated sharply.^{9,10} The NORDIC trial has provided solid evidence that patients can be treated effectively by weight loss and acetazolamide. Their visual acuity and visual fields should be tested

regularly, at a frequency that depends on the severity of their condition. If vision is failing despite medical treatment, rapid surgical intervention is necessary. The 2 main options are lumbo-peritoneal shunt or optic nerve sheath fenestration. Considering all factors, a shunt is usually the best choice,¹¹ although these 2 approaches have not been compared in a randomized clinical trial. Conducting such a trial to determine the best operation for patients with pseudotumor cerebri who need surgical relief of papilledema would be valuable, but may be challenging in terms of patient recruitment and retention. Because relatively few patients with papilledema require surgical intervention, the rate of patient enrollment for a surgical trial might be sluggish. Moreover, the NORDIC trial had a withdrawal rate of 19%, partly because patients with pseudotumor cerebri often face many challenges in life and have a propensity to miss appointments and drop out of treatment.¹²

The NORDIC trial has demonstrated that acetazolamide, along with a weight reduction diet, results in modest improvement in visual field function for patients with mild pseudotumor cerebri. Additional studies are needed to refine the management of patients with pseudotumor cerebri to ensure preservation of visual function.

ARTICLE INFORMATION

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Conflict of Interest Disclosures: None reported.

Funding/Support: National Eye Institute grant EY10217 and EY 02162 and Research to Prevent Blindness.

Role of the Sponsor: The funding agencies played no role in the preparation, review, or approval of the manuscript or the decision to submit the manuscript for publication.

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