Effect of Acetazolamide on Visual Function in Patients with Idiopathic Intracranial Hypertension and Mild Visual Loss (The Idiopathic Intracranial Hypertension Treatment trial).

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This was a multicenter, double blind, randomized, placebo-controlled study of acetazolamide in IIH patients with mild visual loss. Prior, smaller studies had shown the efficacy of weight loss as well as the potential efficacy of weight loss + acetazolamide, though larger trials and added data on the appropriate dosage of acetazolamide for vision improvement was lacking. Hence, the goal of this trial was to determine if acetazolamide + weight loss (i.e., all patients had to also be enrolled in a weight-reduction program which included a low-sodium diet) was effective in reducing or reversing vision loss after 6 months.

Experimental design and statistics: Eligible patient (18-60yrs old) had to meet the modified Dandy criteria for the diagnosis of IIH[1]. In addition, patients were required to have reproducible, mild visual loss (-2 to -7 dB parametric mean deviation (PMD), which is based on the degree of VF loss on HVF testing; more (-) means more VF loss), bilateral papilledema, elevated CSF opening pressure, and no prior treatment for their IIH. Regarding acetazolamide treatment, the study allowed for up-titration of acetazolamide dosing, from an initial dose of 500mg BID to a goal max dose of 4g/day. If patients were ever unable to tolerate their dose of acetazolamide, they were allowed to decrease their dosage to a minimum of 125mg per day. Dosage escalation stopped once each participant's papilledema grade or PMD grade improved. The primary outcome was the change in PMD from baseline to month 6, in the eye with the most severe vision loss at baseline (i.e., the study eye). Examinations were conducted at baseline and then monthly until month 6. The primary outcome was compared between treatment groups via an analysis of covariance, with baseline PMD and papilledema grade (among others) as covariates. Of note, this study only included patients with mild vision loss, as enough investigators felt that patients with more severe vision loss would be eligible for surgery. Therefore, the results of this trial are somewhat skewed towards those with less severe disease.

Results: In terms of baseline characteristics, both the acetazolamide group (N=86) and the placebo group (N=49) had a preponderance of females (> 97%) and a mean BMI of 40; other baseline characteristics were similar. A total of 20% of patients in the acetazolamide group were lost to follow-up, compared to 28% of patients in the placebo group. Of those who completed follow-up, more patients (N=7) discontinued treatment in the acetazolamide group as compared to the placebo group (N=1). While both treatment and placebo groups experienced improvement in PMD over time in the study eye (Fig 2), the mean improvement in the acetazolamide group was significantly larger than in that of the placebo group (p=0.05). Further, the treatment effect was greater in patients with a higher,

[1] Modified Dandy Criteria:
1. Presence of signs and symptoms of increased intracranial pressure
2. Absence of localizing findings on neurologic examination, except for those known to occur from increased intracranial pressure
3. Absence of deformity, displacement, or obstruction of the ventricular system and otherwise normal neurodiagnostic studies, other than evidence for increased cerebrospinal fluid opening pressure (>200 mm water).
4. Abnormal neuroimaging, other than empty sella turcica, optic nerve sheath with filled out CSF spaces, and smooth-walled non-flow related venous sinus stenosis or collapse should lead to another diagnosis
5. Awake and alert patient
6. No other cause of increased intracranial pressure present

baseline level of papilledema (grade of 3-5) as compared to those with a lower baseline level of papilledema (grade of 1-2). The acetazolamide group also had a larger mean improvement in papilledema grade. Finally, participants receiving acetazolamide lost more weight in the 6-month study period as compared to those receiving placebo (p<0.001), despite both groups being in a weight loss program. Through added statistical analyses, however, the study authors were able to attribute a greater percentage of vision improvement to an effect of acetazolamide than to an effect of weight loss in the acetazolamide group. For further secondary analyses that were performed in the study, see Table 3. For a summary of ASEs of acetazolamide, see Table 4. At the conclusion of the trial, the mean dosage of study medication was 2.5g/day in the acetazolamide group and 3.5g in the placebo group.

Conclusions: Overall, the results of this trial suggested that the use of acetazolamide + weight reduction was better than weight reduction/diet alone in terms of vision improvement in patients with IIH and mild vision loss. However, as this study only enrolled patients with mild vision loss and more participants receiving acetazolamide discontinued treatment as compared to placebo, there may have been an undue influence on the treatment effect. However, at the time of publication, this was still a quite significant study, as it was the largest of its kind, and the first randomized, double blind, placebo-controlled study to evaluate the efficacy of acetazolamide for patients with IIH.

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