

What is the optimal dose of acetazolamide in the treatment of idiopathic intracranial hypertension

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Abstract

Objective: Acetazolamide is preferred as the first-line drug for the medical treatment of idiopathic intracranial hypertension. In this study, the efficacy of different doses of the drug on visual functions; visual acuity, optic disc appearance- papilledema grade and visual field-mean deviation (VF-MD) were evaluated. **Methods:** The medical records of 73 patients diagnosed as idiopathic intracranial hypertension based on Modified Dandy Criteria and treated with acetazolamide who were on follow-up between 2010 and 2017 at the Neuro-ophthalmology Unit of Ege University Medical School, Department of Neurology were analyzed. Improvement in the visual functions at the end of the sixth month in three groups taking different doses of the drug; low (500, 750, 1000 mg/day), moderate (1500, 1750, 2000 mg/day) and high (3000, 4000 mg/day) were compared. **Results:** Improvement in visual acuity (p: 0.784), was not affected from different doses of the drug whereas papilledema grade (p: 0.014) and VF-MD (p<0.001) were affected. Binary comparisons revealed significant improvement in the high dose group when compared with the moderate and low dose groups both for the papilledema grade (low-high: p: 0.003, moderate-high: p: 0.024) and VF-MD (low-high: p<0.001, moderate-high: p: 0.001) **Conclusion:** Treatment with high doses of acetazolamide is associated with improvement in visual field defects and regression of optic disc edema in idiopathic intracranial hypertension.

Keywords: Acetazolamide, idiopathic intracranial hypertension, optic disc appearance, visual acuity, visual field

INTRODUCTION

The diagnosis of idiopathic intracranial hypertension (IIH) is based on the presence of raised intracranial pressure without any identifiable pathology in the brain and with normal cerebrospinal fluid (CSF) composition where no underlying etiology is present. Headache is the most common symptom.¹ Papilledema, or optic disc swelling is the hallmark of the disease.² It affects predominantly women at the childbearing age and is typically associated with obesity.¹ Vision loss is the most threatening symptom and has been reported around 90% of patients at presentation. Visual deterioration has been recorded in 10% and total blindness in both eyes in 4% of the patients during follow-up.³ Several medical and surgical therapies have been used to prevent vision loss.

Weight loss is accepted as the only disease-modifying therapy in typical IIH.⁴ Though acetazolamide is generally chosen as the first-line drug for medical treatment a randomized clinical

trial was lacking till 2011. First, the pilot trial of Ball *et al.*⁵ was published with acetazolamide doses ranging from 250 to 1500 mg, followed by the Neuro-Ophthalmology Research Disease Investigator Consortium (NORDIC) IIH Study Group trial to assess the efficacy of weight loss and acetazolamide in treating IIH⁶ where the majority of the patients used acetazolamide between 1 to 4 g/day. A dose comparison was not made in either study and the optimal dose of the drug is still not established.

In this study, we tried to find out the efficacy of different doses of the drug on visual functions including visual acuity (VA), papilledema grade (PG) and visual field (VF) after a treatment period of six months.

METHODS

We retrospectively analyzed the medical records of 73 patients with a diagnosis of IIH based on Modified Dandy Criteria⁷ and treated with acetazolamide for at least six months at the Neuro-

ophthalmology Unit of Ege University Medical School, Department of Neurology. The study was approved by the ethics committee of Ege University Medical School and was performed in accordance with the ethical standards outlined in the Declaration of Helsinki.

The effect of the drug on visual functions was studied. Visual functions taken into consideration were VA in logMAR, PG (optic disc photography was graded from 0 to 3 as follows: Frisén Grade 0 was classified as Grade 0; Frisén Grades 1, 2 as Grade 1; Frisén Grade 3 as Grade 2 and Frisén Grades 4, 5 as Grade 3) and VF (Humphrey automated perimetry, central 30-2 threshold SITA Fast program) mean deviation (MD). For all the visual parameters taken into consideration averaged values recorded from the right and the left eyes of each patient were calculated and used for the statistical analysis. The results of the first visit were compared with the results of the sixth month which was regarded as the last visit. Improvement was the difference between the averaged values of the parameters taken into consideration at the first and last visit. Median acetazolamide dose was 1500 mg/day (min 500, max 4000). The drug was initiated by a tablet (250 mg) given twice daily and the dosage was increased by 1 tablet every other day up to a maximum of 4000 mg if the patients could tolerate. In those who could not tolerate, the dose was lowered in the stepwise fashion used previously by reducing one tablet every other day till the tolerable dose was reached. Three groups taking different dosages were compared: low (500, 750, 1000 mg/day), moderate (1500, 1750, 2000 mg/day) and high (3000, 4000 mg/day).

Statistical analysis

SPSS version 23 (IBM Corporation, Armonk, New York; USA) was used for the statistical analyses. Regarding numerical data conforming normal distribution, arithmetic mean, standard deviation, and 95% confidence intervals (CIs) were used. Data not showing normal distribution were evaluated with non-parametric tests.

Kruskal Wallis Test was used to find if three different doses of the drug had any differences on improvement of the visual parameters taken into consideration. Mann-Whitney U test was used for the binary comparisons of the independent groups.

RESULTS

There were 16 patients in the low, 29 patients in the moderate and 28 patients in the high dose

group. The visual parameters of the three groups at the initial visit and after treatment for six months is given in Table 1 and Figures 1, 2, 3.

VA, PG and VF-MD results recorded in three groups were compared and it was found that improvement in VA ($p: 0,784$), was not affected from different doses of the drug whereas PG ($p: 0,014$) and VF-MD ($p < 0,001$) were affected.

For the improvement in PG and VF-MD binary comparisons (low-moderate, low-high, moderate-high) were studied.

Comparison of the improvement in PG degrees of the low and high those groups was significantly different ($p: 0.003$) showing a better improvement in patients receiving high doses. The same was true for the comparison of the moderate and high dose groups ($p: 0.024$) whereas the comparison of the improvement in low and moderate groups was not significantly different ($p: 0.102$).

Comparison of the improvement in VF-MD values of the patients on low and high doses was associated with a significantly better improvement on behalf of the high dose ($p < 0.001$). Similar result was gathered by comparing the results of patients on moderate and high doses ($p: 0.001$). However, comparison of the improvement in the VF-MD values of patients on low doses with the patients on moderate doses did not reveal a significant difference ($p: 0.061$).

None of the patients experienced serious side effects like aplastic anemia, urolithiasis or significant hypokalemia. However, paresthesias, altered taste, nausea and fatigue were reported by all.

DISCUSSION

Acetazolamide is a carbonic anhydrase inhibitor that reduces CSF production by 6% to 50%.⁸ It has been shown to lower intracranial pressure at doses 3-4g/day.⁹ Paresthesias, dysgeusia, fatigue and gastrointestinal disturbances are very common side effects.

In one of the two previous randomized controlled treatment trials where IIIH patients with mild symptoms and signs were taken into consideration 48% discontinuation at mean doses of 1.5 g/d of acetazolamide was present due to side effects and a significant treatment effect could not be noted.⁵ In the NORDIC IIIH Treatment Trial the use of the drug with a low-sodium weight-reduction diet has been shown to be associated with improvement in VF function in patients with mild visual loss when compared with diet alone at month six.⁶ A significant reduction in PG was also present thought to be related with the reduction

in CSF pressure. Improvement in the nasal and pericecal areas of the VF was associated with regression in PG.^{2,6} It was reported that most of the VF improvement related to acetazolamide took place within the first month of treatment and was greater in patients with moderate to high-grade papilledema.¹⁰ VA was not affected by treatment.⁶ A beneficial effect on CSF pressure¹¹ and positive effects on quality of life measures, particularly neck pain and pulsatile tinnitus has also been reported whereas a benefit on headache severity was not present.^{12,13}

The dosage in this trial was 4g daily, in 44% of the participants. The majority could tolerate 1g/day.⁶

In our study, three different doses of acetazolamide on visual functions were compared. VA was not affected from the usage of higher doses. On the other hand, VF and PG were found to be affected. Significantly better improvement in both the VA and PG was recorded in patients using acetazolamide 3000 to 4000 mg/day when compared with both 500-1000 mg/day and 1500-2000 mg/day. Comparison of 500-1000 mg/day with 1500-2000 mg/day did not reveal a significant difference. Tingling of the hands and feet, altered taste, nausea and fatigue were the side effects reported by all the patients regardless of the dose. The incidence of common side effects has been reported to be the same in both the high and low dose groups in the NORDIC IIH Treatment Trial as well.¹⁴ We cannot give our discontinuation rates as this is a retrospective collection of the data from the medical records of patients who continued treatment for six months which is an important limitation. Papilledema grading was addressed by the same experienced reader (NC) to overcome subjectivity. Automated perimetry is also a subjective measure influenced by physical and behavioral factors. However, the same VF program had been used for all the patients of this study. As far as we could reach no studies are present comparing the efficacy of different doses of acetazolamide on visual functions in IIH.

Our results in favor of using 3000 to 4000 mg/day of acetazolamide in the treatment of visual field defects in IIH need to be supported by further randomized controlled trials.

DISCLOSURE

Financial support: None

Conflict of interest: None

Table 1: The visual parameters of the three groups of patients at the initial visit and after treatment

Doses	Number of Patients	Visual Parameters	Initial Visit	Final Visit	Mean Improvement	Standart Deviation	Minimum	Maximum
500-750-1000	16	Visual acuity in logMAR	0,066	0,019	0,047	0,083	-0,023	0,224
		Papilledema grade	1,313	0,730	0,583	1,276	-1,000	3,000
		Visual field mean deviation	-6,940	-4,640	2,296	1,620	0,420	7,640
1500-1750-2000	29	Visual acuity in logMAR	0,043	0,005	0,038	0,106	-0,026	0,460
		Papilledema grade	1,569	0,964	0,605	1,264	-1,000	3,000
		Visual field mean deviation	-7,320	-3,730	3,598	3,020	0,610	12,960
3000-4000	28	Visual acuity in logMAR	0,112	0,043	0,069	0,150	-0,072	0,540
		Papilledema grade	1,675	1,033	0,672	1,106	-2,000	1,000
		Visual field mean deviation	-7,850	-2,190	5,659	2,140	1,550	8,780

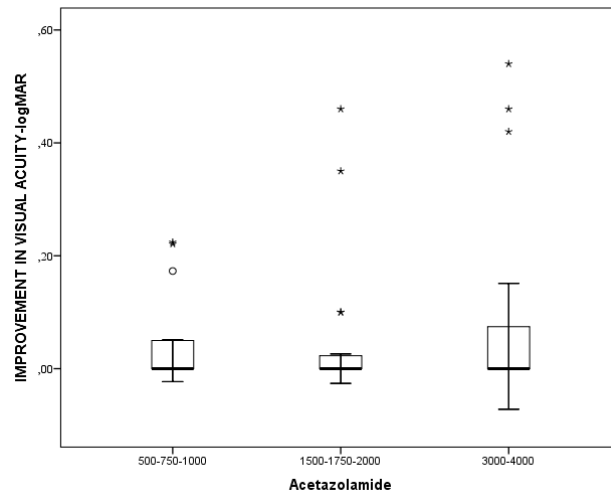


Figure 1

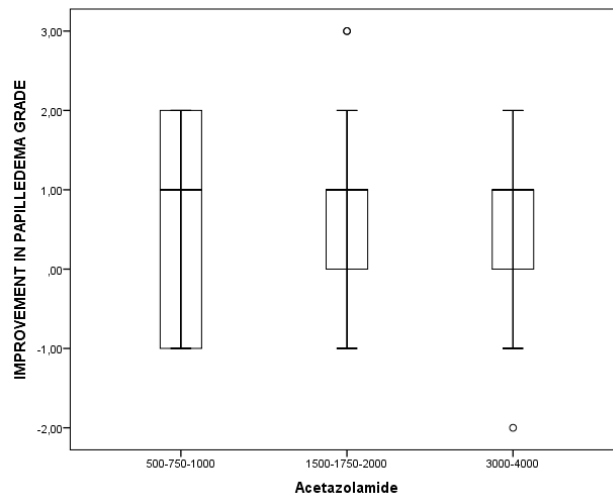


Figure 2

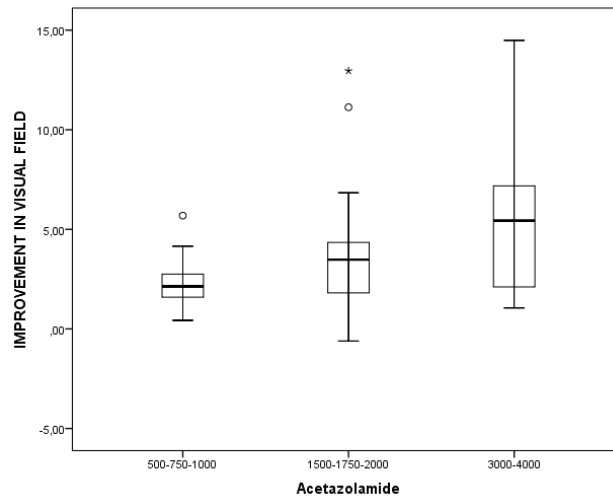


Figure 3

Ethics: The present study was approved by the Ethics Committee of Ege University Medical School (date: 23.07.2018 ref number: 58153)

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