Long-Term Effect of Acetazolamide in a Patient with Retinitis Pigmentosa

J. C. Chen,* F. W. Fitzke,† and A. C. Bird*

The authors studied the therapeutic effect of acetazolamide on a patient with autosomal dominant retinitis pigmentosa complicated by retinal edema. In addition to reduction of macular edema and some improvement of central vision, they found an unexpected progressive increase in extrafoveal retinal sensitivity with prolonged medication. It is proposed that the therapeutic effect is mediated by alteration of retinal pigment epithelial function and that disturbed polarity is restored to a more normal state. Invest Ophthalmol Vis Sci 31:1914-1918, 1990

In retinitis pigmentosa (RP) central vision is usually preserved until late in the disease unless macular edema supervenes. Recently, it has been demonstrated that acetazolamide, a carbonic-anhydrase inhibitor, can increase visual acuity in certain patients with RP and macular edema.1,2 Some of our patients have claimed major subjective improvement in vision but without significant change of visual acuity. In one such patient we investigated the nature of the visual improvement in detail.

Case Report. A 48-year-old white woman with autosomal dominant RP had night blindness for as long as she could remember and progressive loss of visual field over the previous 2 yr. Central vision had been poor in the right eye (OD) for many years and in the left (OS) for 1 yr. On examination, her visual acuity was hand motions OD and 6/18 OS. Anterior segments of both eyes were normal. Both ocular fundi showed pale optic discs, narrow, straightened retinal blood vessels, and diffuse pigmentary disturbance in the midperiphery with few typical bone spicules, limited to the equatorial fundus. Macular edema with large cyst-like spaces was more marked OD than OS. Fluorescein angiography showed leakage of dye into the outer retina, which appeared to be derived from the choroid through the retinal pigment epithelium (RPE).

The severe visual loss in the patient and in two of her three affected sons precluded subclassification of the disease. Her youngest son, aged 15 years, had substantial visual field loss affecting both rods and cones. However, rod loss was widespread and greater than 2 log units throughout the central 30°; in some locations cone loss was less than 1 log unit. The difference in rod and cone sensitivities in the youngest son, together with the sequence of symptoms and relative paucity of pigment migration in the patient despite a long history of symptoms, suggest that the family had "diffuse" or "type 1+4,5 RP.

After a 2-week course of acetazolamide 500 mg/day, the patient reported marked improvement in vision; everything appeared brighter, and she could see in dim illumination. This was followed by subjective worsening of vision after withdrawal of treatment. However, her acuity changed little.

To verify her claim of subjective visual improvement, she received acetazolamide over a 3-month period during which visual acuity, visual sensitivity, and fluorescein angiography were recorded (Table 1).

Materials and Methods. Psychophysical testing was done OS since the better acuity in this eye allowed more reliable fixation. After pupil dilation and dark adaption for 45 min, scotopic thresholds were measured using a modified central 30-2 program of the Humphrey automated perimeter.6 The background illumination was turned off, the Humphrey blue filter (with a 1.2-log unit neutral-density filter) or the Humphrey red filter was placed in the stimulus beam to assess the relative function of the rod and the cone systems. Stimulus size V was used. An infrared source, illuminating the bowl and eye position, was monitored with an infrared CCD camera.

Fine-matrix mapping was done with an apparatus which uses a television screen to present blue flashes under scotopic conditions.7,8 Fixation was achieved with a red light-emitting diode. For the current study, sensitivity was tested at 100 positions on a 10 × 10 square matrix over a 20 × 20° test field, and stimuli were presented at 2° intervals with each stimulus subtending an arc of 10 min. The test field was centered 10° above and nasal to fixation. Subsequent processing of the data produced a three-dimensional representation of rod thresholds—the higher the elevation from baseline, the greater the loss of function compared with established normal values.

Results. There was little improvement in either Snellen acuity (one line) or the foveal threshold OS.
Summary of management, visual acuities and left eye Humphrey perimeter results

Table 1. Summary of management, visual acuities and left eye Humphrey perimeter results

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Acetazolamide dosage (mgs)</th>
<th>Acuity</th>
<th>Sensitivity</th>
<th>Test points seen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Foveal</td>
<td>Parafoveal</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Red</td>
<td>Blue</td>
</tr>
<tr>
<td>0</td>
<td>None</td>
<td>HM</td>
<td>6/18</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>1000</td>
<td>6/60</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>10</td>
<td>None</td>
<td>5/60</td>
<td>37</td>
<td>21</td>
</tr>
<tr>
<td>14</td>
<td>1000</td>
<td></td>
<td>28</td>
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<td></td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>22</td>
<td>1000</td>
<td>6/36</td>
<td>23</td>
<td>20</td>
</tr>
</tbody>
</table>

* Daily dose of Acetazolamide at time of test visit.
† Foveal and parafoveal scotopic sensitivities as measured by modified Humphrey perimeter using red and blue stimuli.
‡ This test was performed last in the series, and, unlike other visits, the patient underwent clinical examination prior to testing. The consequent exposure to lights and resulting fatigue may have contributed to the low number of test points seen at this visit.

throughout the treatment period (Table 1). Acuity improved from hand motions OD to 6/36. The macular edema improved, and the dye leakage diminished on fluorescein angiography, but the cystoid spaces at the fovea remained.

There was small-to-moderate improvement in scotopic retinal function at four testing positions closest to fixation on the Humphrey 30-2 program (Table 1). With prolonged treatment, there was gradual improvement in nonfoveal sensitivity by as much as 2 log units (Fig. 1).

Although there was some fluctuation in the area recorded by fine-matrix mapping, overall there was progressive improvement of more than 2 log units in scotopic sensitivity in the superonasal paracentral visual field during the course of treatment (Figs. 2, 3). There was good concordance between the results in the superonasal visual field with the two test systems (Figs. 1A, B correspond with 2A, and Figs. 1D, E with 2F).

Discussion. As previously demonstrated,\(^1,2\) acetazolamide caused resolution of the macular edema, although the therapeutic mechanism is uncertain. It has been postulated that retinal edema in RP is due, at least in part, to a disturbance of the normal RPE polarity whereby the RPE moves ions, and therefore water, constantly from the neuroretina toward the choroid.\(^1\) This suggestion was made on the basis of the finding that fluorescein is seen to enter the outer retina from the choroid during fluorescein angiography in some patients with RP and retinal edema.\(^5,10\)

The observation that cellular polarity, as shown by protein sorting, may be influenced by transcellular and transmembrane pH gradients\(^11\) led to the concept that acetazolamide may restore polar function by modulating ionic movements across the RPE cell membrane with consequent changes in transmembrane pH gradients. That the therapeutic effect may be due to alteration of RPE function, is supported by two additional observations. Acetazolamide does not enter the neuroretina readily,\(^12\) so that it would have free access only to the carbonic anhydrase on the basolateral membrane of the RPE. Furthermore, there is some selectivity in the therapeutic response of macular edema, in general, to acetazolamide, treatment being most effective in those disorders in which the RPE, rather than the retinal capillaries, appears to be the major source of the edema fluid.\(^1\) However, an effect on the retinal capillaries cannot be discounted as contributing to the therapeutic effect since leakage from retinal blood vessels has been observed in some patients who responded to treatment, and retinal vessel leakage may be modified during the course of therapy.

Previous observations on macular edema have shown a rapid increase in visual acuity as the edema subsides.\(^1,2\) The change in visual function may be due to restoration of more normal ionic concentrations in the interphotoreceptor space. In our patient increased visual acuity may have been limited by permanent structural damage (implied by persistent cystoid change at the fovea). The increase in acuity OD was probably due to a change in parafoveal retinal function.

More interesting is the gradual improvement in the patient’s general scotopic function, as measured both by Humphrey and fine-matrix perimetry over a 3-month period. This improvement extended to as much as 30° from fixation and, in certain test positions, was as much as 3 log units. Our observation may parallel those of Fishman et al.:\(^2\) considerable subjective and objective improvement in vision occurred without change in the edema. This led to the suggestion that visual recovery may reflect the influence of acetazolamide on metabolic functions other than movement of ions and water.\(^2\) Disturbed polar-
Fig. 1. Gray scale (A) and numeric representation in decibels of the scotopic retinal sensitivity to red (B) and blue (C) stimuli at 10 weeks and 24 weeks (D, E, F). The appearance of lighter shading centrally (A–D) implies recovery of function in the central visual field. Comparing (B) to (E), the sensitivity in the parafoveal area (out to 3° visual angle from fixation) has improved from 5–9 dB to 16–20 dB, while areas in the peripheral macula have changed from unrecordable to 20 dB, representing an improvement of at least 2 log units (see table I).
Fig. 2. Scotopic retinal threshold elevation from fine matrix perimetry in the superonasal 20° × 20° field at 10 weeks (A), 14 weeks (B), 18 weeks (C), 20 weeks (D), 22 weeks (E) and 24 weeks (F) (see Table 1). The x and y axes represent retinal location, and interval between each tic mark on the axes is approximately equivalent to 2.1° of visual angle or about 600 μm on the retina. Average threshold values of normal volunteers is given a value of 0, and elevation above the baseline represents loss of threshold. The gradual fall of the threshold profile towards the baseline indicates recovery of sensitivity over a large area of the posterior retina.
ity of the RPE may have an influence upon directional inward transport of important metabolites, such as fatty acids and retinoids, from the choroid to the neurosensory retina and outward disposal of metabolic products. If receptor dysfunction were due at least in part, to abnormal delivery and disposal of such metabolites and restoration of RPE polarity by acetazolamide corrected the abnormality, functional recovery might be slow once normal exchange were restored since restoration of outer segment stability may take several weeks after sustained metabolic insult.

Our results show that the visual loss recorded initially in this patient was not due to cell death but was a consequence of a reversible metabolic dysfunction. It is not known whether the visual function recovered in this case is related to manipulation of the primary metabolic defect or a secondary response to the disease. Edema occurs in several forms of RP, implying that the latter is more likely. The concepts derived from these clinical observations should be amenable to testing in cell preparations, animals, and humans.

It is evident that observations of a single case do not allow therapeutic recommendations to be made, and further studies are necessary to establish the role of acetazolamide in the management of RP. Observations in this patient are relevant to any such study. They show that recording visual acuity and change in the edema over the short periods used in the original study are inadequate to test the full therapeutic effect of carbonic-anhydrase inhibition. Longer trials and more complete psychophysical measurement are required. Acetazolamide is not an ideal drug since there are many side effects, and better therapeutic agents are needed.

Key words: retinitis pigmentosa, macular edema, acetazolamide

From the Departments of Clinical Ophthalmology and Visual Science, Institute of Ophthalmology, University of London, London, England. Supported in part by the Wellcome Trust, the National Retinitis Pigmentosa Foundation, and The British Retinitis Pigmentosa Society. Dr. Chen received a fellowship from the McLaughlin Foundation Canada. Reprint requests: A. C. Bird, Professorial Unit, Moorfields Eye Hospital, City Road, London EC1V 2PD, England.

References

Fig. 3. Mean and I standard deviation of sensitivities on fine matrix perimetry during the period of prolonged treatment from week 10 corresponding to Figure 2A-F.