The long-acting Ocusert-pilocarpine system in the management of glaucoma.* Pei-fei Lee, Yeong-tai Shen, and Marilyn Eberle.

The Ocusert-pilocarpine devices with seven days' therapeutic duration were compared with pilocarpine eye drops for efficacy and ocular tolerance in the management of glaucoma in 16 patients. Magnitude of pressure reduction with release rates of 20 meg. and 40 meg. of pilocarpine per hour were as effective in the treatment of glaucoma as 2 per cent and 4 per cent pilocarpine eye drops, respectively. Ocular tolerance and retention in the human eyes were good. There were no appreciable side effects other than the occasional sudden leakage phenomenon encountered. Further refinement of the Ocusert-pilocarpine device to reduce the incidence of leakage would not only ensure precision in the rate of drug release, but would also expand its clinical application.

Initial clinical investigation and the details concerning the Ocusert-pilocarpine system have been reported by others. Ocusert-pilocarpine devices which can maintain a therapeutic duration up to four days have also been reported.* The purpose of this communication is to report the therapeutic effect of allowing the Ocusert-pilocarpine device to remain in the conjunctival cul-de-sac for a period of seven days. The long-lasting effect and safety of the Ocusert-pilocarpine system and the comparison of the Ocusert-pilocarpine device with pilocarpine drops for efficacy and ocular tolerance in the management of glaucoma were also evaluated.

Materials and methods. Two types of Ocusert devices, programmed at different pilocarpine release rates (P-20 and P-40), were used in this study. P-20 provided a pilocarpine release rate of 20 meg. per hour and 40 meg. per hour for P-40, both of which lasted at least seven days. A single Ocusert device was allowed to remain in the conjunctival cul-de-sac for a period of seven days. Periods longer than seven days were not evaluated in this study. For a uniform clinical evaluation of the Ocusert-pilocarpine system, Protocol OPI-3-03 prepared by the manufacturer was used for this study.

Sixteen pilocarpine-responsive glaucoma patients (13 open-angle and three residual-angle-closure glaucoma patients after surgery) were selected for this study. Patients' ages ranged from 23 to 70 years. Previous concurrent medication was continued during this study, while the pilocarpine eye drops were replaced by the Ocusert-pilocarpine device. Throughout the course of this study, the ocular pressure was measured by applanation tonometry two to five hours after the last eye drop instillation, or on the fourth and seventh days of Ocusert wearing. At the time this report was prepared, each patient was asked the following questions: (1) what was his feeling about the Ocusert device and (2) would he like to go back to the pilocarpine eye drops?

Ocular tolerance to the Ocusert device was evaluated with slit lamp biomicroscopy, ophthalmoscopy, and visual field. During each visit, examination of visual acuity, pupil size, Ocusert condition, and external eye's condition by slit lamp biomicroscopy were made. The results were recorded at each visit on special forms prepared for this study. Whenever the Ocusert was lost or twisted inside the conjunctival cul-de-sac, it was replaced with a new one. All patients were instructed to check the presence of the Ocusert twice daily to ensure continuous drug delivery. Visual fields and ophthalmoscopy were repeated every eight weeks or at every other visit during the extended period of the study. Optic disc photographs were also utilized selectively in evaluating the status of glaucoma.

Results. Sixteen patients (30 eyes) who were able to fulfill the Ocusert-pilocarpine study were included in this report. One glaucoma patient (two eyes) was excluded from the study because he was unable to complete the investigation. The follow-up period ranged from six to nine months, and the study is continuing. In general, the Ocusert-pilocarpine device was satisfactory for glaucoma control, well tolerated, and its presence was usually unnoticed by the patients. The Ocusert device sometimes remained in the lower cul-de-sac of the conjunctiva, but often moved to the upper cul-de-sac or canthus regions, especially during the sleeping hours.

Intraocular pressure reduction. Data obtained from a total of 28 eyes (15 patients) were utilized for pressure analysis. Twenty-six eyes showed sustained decreases in intraocular pressure below the 22 mm. Hg level. The mean pressure in 26 eyes was 17.81 ± 2.11 at the end of the fourth month and 19.44 ± 2.50 in 18 eyes at the end of the ninth month. The mean pressure was 19.21 ± 2.50 in the right eye and 17.90 ± 2.32 in the left eye. The remaining two eyes (two patients) developed resistance after the fourth and sixth weeks of Ocusert treatment, respectively. Their pressures were under control again after an increase in the concentration of epinephrine hydrochloride in one patient and the addition of acetazolamide to the medication in the other. These two eyes were excluded in the pressure analysis at the end of the fourth month but were included in the ninth month results. The mean pressures with pilocarpine eye drops were 20.52 ± 2.59 in the right eye and 19.11 ± 2.33 in the left eye. In general, the therapeutic value of the Ocusert P-20 is equivalent to a pilocarpine eye drop concentration...
Table I. Mean pressure reduction in 26 glaucomatos eyes showed sustained pressure control with Ocusert-pilocarpine system

<table>
<thead>
<tr>
<th>Average intraocular pressure (mm. Hg) on fourth and seventh days of Ocusert-pilocarpine</th>
<th>Second month</th>
<th>Third month</th>
<th>Fourth month</th>
<th>Standard deviation of the mean</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eye</strong></td>
<td><strong>1st week on Ocusert-pilocarpine</strong></td>
<td><strong>2nd week</strong></td>
<td><strong>3rd week</strong></td>
<td><strong>4th week</strong></td>
</tr>
<tr>
<td>OD</td>
<td>18.00</td>
<td>18.00</td>
<td>18.00</td>
<td>17.41</td>
</tr>
<tr>
<td></td>
<td>±2.65</td>
<td>±2.95</td>
<td>±2.76</td>
<td>±3.14</td>
</tr>
<tr>
<td>OS</td>
<td>17.76</td>
<td>18.30</td>
<td>17.69</td>
<td>17.76</td>
</tr>
<tr>
<td></td>
<td>±3.11</td>
<td>±3.29</td>
<td>±3.11</td>
<td>±3.20</td>
</tr>
</tbody>
</table>

Clinical evidence of therapeutic resistance to the Ocusert-pilocarpine device encountered (two eyes) was not conclusive.

Ocular tolerance and complications. Sudden leakage or burst phenomenon of the Ocusert-pilocarpine device occurred in four eyes (three patients) with open-angle glaucoma. Signs and symptoms which were associated with the burst phenomenon were sudden and severe decrease in vision, extreme miosis, further decrease in pressure (Fig. 1), cooling and burning sensations, and mild congestion of the conjunctiva. Two of these three patients experienced repeated burst phenomena. Eight eyes (four patients) experienced transient blurring of vision during the first day of Ocusert-pilocarpine, following which a reasonably stable vision was maintained. The initial transient blurring of vision was usually associated with a more miotic pupil and was related to the early hours' release of pilocarpine, not the burst phenomenon. Mild but consistent tearing occurred in eight eyes of four patients. Tearing was usually experienced early in the morning either before or soon after waking. However, all patients were satisfied with the Ocusert-pilocarpine device and wished to continue the study. None of the 15 patients were dropped from the study because of the side reactions described. Two patients experienced headaches with pilocarpine eye drops but no longer experienced any after the switch to the Ocusert-pilocarpine device. Repeated detailed ocular examination including indirect ophthalmoscopy, biomicroscopy, and visual fields during the follow-up period revealed no serious complications in any eye.

Discussion. Clinical results have confirmed the studies by others\(^a\) that the Ocusert-pilocarpine devices programmed for a constant rate of drug delivery are therapeutically effective in the management of glaucoma and have great advantages over the current methods of pulsed medication. Ocusert devices probably represent the only practical method which can provide a continuous, constant, steady-state of drug delivery to the eye.
The retention of the Ocusert-pilocarpine device and its acceptability to patients were satisfactory. The conventional methods of using eye drops of various vehicles, ointment, drug-soaked hydrophilic contact lens, and the micropump system have not, in any practical way, provided a true zero order of delivery rate to the eye. The micropump system is superior to eye drops, but it is inconvenient and expensive. The drug-soaked soft contact lens provides a first order of drug delivery. The first order of delivery rate or pulsed medication is not constant and produces either over- or under-treatment. In general, the intraocular pressure was better controlled with the Ocusert-pilocarpine device than with conventional pilocarpine eye drops (Table II).

A dose-response study of the Ocusert-pilocarpine device showed an increase in the pressure-lowering effect with an increased Ocusert release rate of pilocarpine. A rather rapid release of pilocarpine occurs during the initial hours of the Ocusert placement, indicating that a continuous release rate is not equivalent to a constant release rate. While it is releasing the pilocarpine, a sudden leakage or burst phenomenon has occurred in some patients. The short-lasting burst phenomenon is of clinical importance even though the therapeutic effect was not diminished. The burst phenomenon described above is defined as a sudden, marked, short-lasting leakage of the Ocusert system or rapid release of pilocarpine which occurs sometime during the seven-day period, not during the initial hours of wearing. It usually occurs during the sleeping hours or early in the morning. This phenomenon should not be confused with the initial release of the drug by the Ocusert system. The symptoms and signs induced by the burst phenomenon were marked decrease in vision, extreme miosis, significant further decrease in intraocular pressure (Fig. 1), and cooling and burning sensations with mild conjunctival congestion and headaches. Analyses for possible deficiencies in the Ocusert-pilocarpine devices were performed by the manufacturer and the results were not significant. It should be emphasized that ocular effects produced by the amounts of pilocarpine released in the sudden burst are greater than those caused by 4 per cent pilocarpine eye drops. Therefore, the negative analyses' results may indicate that the method used in the assay is insufficient, and a better method for the analysis of drugs contained in the Ocusert device is needed. The sudden unpredictable release of a large amount of drug may limit the Ocusert system in clinical application, especially when a more potent drug is used. So far, no retinal detachment, pupillary block, or other related complications have been encountered.

The overall incidence of sudden leakage phenomenon ranging from 0 to 0.7 per cent has been observed by others. In this series, the incidence of leakage phenomenon observed is 1.6 per cent. Discrepancies among investigators is probably related to the individual patient's physical condition and environment. It is, however, unexplained at present, but raises some intriguing theoretical, as well as practical, questions.

Another point which deserves attention is that it is impossible to identify P-20 and P-40 once they become mixed up. Clinically, it is not unusual to see that the status of glaucoma and medication required can be different between two eyes of the same individual. Therefore, for practical reasons, it would be more desirable if the Ocusert P-20 and P-40 could be easily differentiated by the patient, either by making variable sizes or by coloring the sealing bands around the Ocusert devices. The Ocusert-pilocarpine device with a predetermined release rate will undoubtedly ensure adequate treatment at night and will reduce the pressure diurnal variation peaks. Patients evaluated in this series found the Ocuserts more practical than the frequent instillation of drops. If a smaller amount of pilocarpine is needed to control the pressure with the Ocusert than with the drops, fewer topical and systemic side effects would be expected to occur. This has been our experience with the patients studied. Pupil size and accommodation evaluation, as well as pupil size and pressure level evaluation, were not attempted in this series. In general, miotic pupil diameter was approximately 0.5 mm. to 1.0 mm. larger with the Ocusert-pilocarpine device than with pilocarpine eye drop medication. This observation is in agreement with others and is beneficial in patients with cataract and refractive errors.
The advantages of the Ocusert-pilocarpine devices far outweighed the disadvantages. The main advantages are: (1) constant and continuous delivery of the drug which provides better pressure control and round-the-clock protection; (2) convenience to the patient, especially elderly persons and patients in nursing homes; (3) favorable pattern of myopia and miotics; (4) less chance of forming posterior synechia of iritis; and (5) easier dilation of pupil with mydriatics.

It is emphasized that a large series of patients with various types of glaucoma and long-term follow-ups are needed. Laboratory and clinical data which have been collected by the manufacturer should be carefully evaluated, so that clinical indications and contraindications for the Ocusert-pilocarpine devices can be defined. Deficiencies in the current Ocusert system may be further refined. Liberalization now on clinical application of Ocusert containing more potent drugs would be premature.

Ocuserts used in this study were developed and provided by the ALZA Corporation, Palo Alto, Calif. The authors wish to thank the following persons for referring their patients for this study: Doctors Mark Levy, Aaron Kassoff, Robert Reinecke, and Peter Kansus.

From the Department of Ophthalmology, Albany Medical College of Union University, and the Section of Ophthalmology, Surgical Service, Veterans Administration Hospital, Albany, N. Y. Supported in part by the National Institutes of Health Training Grant No. EY-00044 and in part by the ALZA Corporation. Submitted for publication May 3, 1974. Reprint requests: Dr. P. Lee, Department of Ophthalmology, Albany Medical College, Albany, N. Y. 12208. *This paper was presented at the Association for Research in Vision and Ophthalmology, April 29, 1974, Sarasota, Fla.

Key words: glaucoma treatment, pilocarpine, Ocusert system, clinical evaluation.

REFERENCES


Aqueous humor dynamics, visual fields, optic discs, anterior chamber angles, and topical corticosteroid responsiveness were studied in twenty parents of children having primary congenital glaucoma. The findings indicate that parents of children with primary congenital glaucoma resemble the general population with respect to the parameters tested, and do not resemble close relatives of patients with primary open-angle glaucoma.

Primary congenital (infantile) glaucoma is thought to be inherited as an autosomal recessive trait. Studies of the intracranial pressure (IOP) response to topical corticosteroids in patients with primary open-angle glaucoma and their relatives suggest that this disease may also have a recessive mode of inheritance. Furthermore, topical corticosteroids may induce glaucoma in the eyes of susceptible infants, just as in susceptible adults. The question, therefore, arises as to whether a genetic relationship exists between primary congenital and primary open-angle glaucoma.

Patients with primary open-angle glaucoma differ from the general population in terms of elevated IOP, decreased facility of aqueous outflow (C), pathologic cupping of the optic nerve head, and characteristic visual field loss. They also demonstrate a rise in IOP and a fall in C after the topical application of corticosteroids, or after water drinking. Intermediate or high IOP responses to topical steroids, and high tonographic Po/C ratios after water drinking are also more prevalent in relatives of patients with primary open-angle glaucoma than in the general population.

These latter parameters cannot be readily tested in glaucomatous infants, but can be studied in their parents. Accordingly, parents of children with primary congenital glaucoma were studied with respect to their aqueous humor dynamics, visual fields, optic cup/disc diameter ratios, and IOP response to topical corticosteroids to see if they most closely resemble the general population or the close relatives of patients with primary open-angle glaucoma.

Materials and methods. Twenty parents of children with primary congenital glaucoma were