Pilocarpine: The Frequency Dogma

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Pilocarpine, a cholinergic agonist, reduces intraocular pressure by stimulating postsynaptic muscarinic receptors in the ciliary muscle causing it to contract. Pilocarpine preparations have been used since the 1870s, but the need to administer them frequently everyday has made them unsuitable for many patients.¹ The optimal strength and frequency of administration of pilocarpine for control of intraocular pressure has not been scientifically defined. The purpose of this investigation, was to evaluate the effect of varying frequency of pilocarpine hydrochloride 2% on IOP.

This study was approved by the Wills Eye Institute Institutional Review Board (IRB#08-914E). Informed consent was obtained prior to the initial screening evaluation. This was a prospective analysis of patients aged 18 years or older with open angle glaucoma or open angle glaucoma suspects. Patients were selected from glaucoma service of Wills Eye Institute. Patients were either naïve to glaucoma therapy or administering topical medications other than long acting miotics. Patients were excluded from the study if they had coexisting ocular pathology, recent ocular surgery, or ocular inflammation or ocular infection within 3 months prior to the screening visit, previously recorded allergy to pilocarpine, pregnant women or nursing mothers.

The study included 15 patients with demographic data detailed in Table 1. At the start of the study the following attributes were checked: visual acuity, color of the iris (blue, brown or hazel), size of the pupil, IOP measurement by Goldmann applanation tonometer (P_0), gonioscopy for nature of the chamber angle, slit-lamp biomicroscopy using a +66D lens for cup-to-disk ratio, depth of the cup and degree of pallor of the disk and visual field by Humphrey field analyzer (Carl Zeiss Meditec, Inc.). A 4 minutes pressure tracing was obtained with a needle recorder attached to the indentation tonometer while it was gently applied to the cornea. Its position on the cornea was maintained until a smooth tracing for 4 minutes was obtained. The P_0 and the change in scale reading during the 4 minutes were then used to obtain the coefficient of outflow facility (C) from tonographic Tables.²

All medications were stopped for thirty days. On the fourth day, intraocular pressure was measured at 9 am, 12 pm and 5 pm to determine the daily variation off treatment. Pilocarpine 2%

Table 1: Patient demographics

Patients enrolled	15
Age range (in years)	36-74
Race	
• African-Americans	12
• Euro-Americans	3
Diagnosis	
• POAG	14
• POAG suspects	16

was started in both eyes on the fifth day. On day 5 through 8, each patient was instructed to take pilocarpine once daily in the right eye at 10 pm, and twice daily in the left eye (10 am and 10 pm). On days 9 through 11, pilocarpine was again administered once daily in the right eye at 10 pm, but was increased to four times daily in left eye (8 am, 1 pm, 6 pm and 10 pm). On days 12 through 15 the program was reversed, pilocarpine being given four times daily in the right eye and once daily in the left eye. On days 16 through 18 the program was again reversed, pilocarpine now being used four times daily in the left eye and once daily in the right eye. On the last three days of the study, 19 through 22, this was again reversed, pilocarpine now being used four times daily in the right eye and once in the left eye. Following the 10 pm dosage on day 22 no medication was used for three days. Intraocular pressure was taken at 9 am, 12 pm and 5 pm on days 4, 8, 11, 15, 18, 22 and 25. Thus the frequencies employed were one, two and four times daily in each patient, and intervals tested were 1, 2, 4, 7, 11, 14, 19, 59, 62 and 67 hours post-therapy. The total duration of the study was twenty-five days. Study protocol is described in Table 2.

The mean IOP with different frequency of administration of pilocarpine 2% are shown in Table 3. The coefficient of outflow ranged from 0.50 to 0.30. Statistical analysis revealed that four times daily administration resulted in significantly lower tension compared to daily or twice daily treatment. The mean IOP obtained with twice daily treatment was slightly lower when compared to the mean IOP on once daily treatment. However, the difference was not statistically significant. There was no significant difference in the mean IOP between the two periods of no treatment. Table 4 summarizes the mean IOP taken at 9 am, 12 pm, and 5 pm on different frequencies of pilocarpine 2%. On

Table 2: Study protocol

Visit	Regimen	Duration
Screening	Washout of medications, if necessary	30 days
1; Baseline	Detailed workup	D0
2	Pilocarpine 2% OU (IOP measured @ 9 am, 12 pm, 5 pm)	D4
3	Pilocarpine 2% OD: qpm @ 10 pm OS: bds @ 10 am, 10 pm	D5-D8
4	Pilocarpine 2% OD: qpm @ 10 pm OS: qds @ 8 am, 1 pm, 6 pm, 10 pm	D9-D11
5	Pilocarpine 2% OD: qds @ 8 am, 1 pm, 6 pm, 10 pm OS: qpm @ 10 pm	D12-D15
6	Pilocarpine 2% OD: qpm @ 10 pm OS: qds @ 8 am, 1 pm, 6 pm, 10 pm	D16-D18
7	Pilocarpine 2% OD: qds @ 8 am, 1 pm, 6 pm, 10 pm OS: qpm @ 10 pm	D19-D22
8	None for D23-D25, Exam on D25	D25

Table 3: Mean intraocular pressure in relation to frequency of administration of pilocarpine 2% given for a period of three days

Frequency	Mean IOP $\pm$ SD (mm Hg)	Effect
None	26.4 $\pm$ 3	—
Once daily	22.6 $\pm$ 2.3	-3.8
Twice daily	21.3 $\pm$ 2.9	-5.1
Four times daily	17 $\pm$ 1.9	-9.4

Table 4: Diurnal variation of intraocular pressure in relation to frequency of administration of pilocarpine 2%

Time	IOP at 9 AM (mm Hg)	IOP at 12 PM (mm Hg)	IOP at 5 PM (mm Hg)
Once daily	22.4 $\pm$ 2.6	22.6 $\pm$ 2.3	22.8 $\pm$ 2.4
Twice daily	21.2 $\pm$ 3.1	21.7 $\pm$ 3.2	21.2 $\pm$ 2.6
Four times daily	17.2 $\pm$ 1.8	17.0 $\pm$ 2.0	16.9 $\pm$ 2.7

chronic administration, a single daily dose caused a persistent lowering of IOP of about 4 mm Hg.

Effectiveness of pilocarpine 2% at various intervals after administration is shown in Table 5. On comparing once daily versus twice daily administration at eleven hours post-therapy, the difference in effect was 1.3 mm Hg.

Fifty-nine hours after the last drug administration there was no hypotensive effect evident. Fifty-nine, 62 and 67 hours post therapy the mean IOP of eyes last treated with a four times daily administration of pilocarpine 2% were similar to the mean IOP of those eyes last treated with the frequency of once daily.

Our study showed that the administration of pilocarpine 2% once daily has a hypotensive effect of about 4 mm Hg which persists throughout the day. Increasing the frequency of administration, but keeping the concentration constant, causes additional hypotension. There appears to be a cumulative action with repeated instillations of pilocarpine.³

The prolonged effect of a single dose of pilocarpine 2% has apparently not been documented experimentally before. Harbin et al showed that pilocarpine, when given twice daily lowered

Table 5: Intraocular pressure in relation to interval between administration of last drop and time of pressure measurement

Intervals post-treatment	Mean IOP (mm Hg)
11 hours (once daily)	22.8
14 hours (once daily)	22.6
19 hours (once daily)	22.8
2 hours (twice daily)	21.7
7 hours (twice daily)	21.2
11 hours (twice daily)	21.1
1 hour (four times daily)	17.2
4 hours (four times daily)	16.9

IOP, though not as effectively as when given four times daily.⁴ Quigley and Pollack found what they considered an inadequate clinical effect when pilocarpine was administered twice daily.⁵ However, our experience with patients in which pilocarpine was administered for a longer experimental period suggested that some individuals who are markedly responsive to the hypotensive action of pilocarpine may demonstrate a persistent fall of IOP of 8 mm Hg, an amount that can be expected to be clinically beneficial. It has been demonstrated by Worthen that pilocarpine treatment reduces the diurnal variation of IOP of patients with glaucoma as well as lowers the mean IOP.⁶

Pilocarpine penetrates the cornea well.^{5,7} While the kinetics and distribution of pilocarpine within the eye have been studied the exact mode by which the drug metabolises is not fully understood.^{8,9} Enzymatic hydrolysis of pilocarpine, which occurs in serum and liver, may not be an important factor in the eye.¹⁰⁻¹² The relatively prolonged action of pilocarpine may be related to storage of the drug in ocular tissues. Van Hoose and Leaders have suggested that pilocarpine may be stored within the cornea, which may then serve as a drug reservoir.⁷ Several investigators have demonstrated binding of pilocarpine to intraocular tissues. Newsome and Stern demonstrated that pilocarpine can be released from ocular tissue and is not destroyed enzymatically.¹⁰ Harris and coworkers demonstrated that pilocarpine was difficult to wash from iris tissue.¹³ Lyons and Krohn noted that pigmented uveal tissue of the rabbit took

up two to three times more pilocarpine than did nonpigmented tissue.¹⁴ In the present study there was no apparent difference in responsiveness between the Afro Americans and the Euro American patients, but, as there were only three Euro-Americans, no valid conclusions in this regard can be drawn.

To summarize, pilocarpine 2% administered twice daily, will lower IOP effectively in many patients with glaucoma.

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“Love is the only freedom in the world because it so elevates the spirit that the laws of humanity and the phenomenon of nature do not alter its course.”

— Kahlil Gibran