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Case Report

Nocturnal Effects of Pilocarpine on Intraocular Pressure: A Case Report Using a Contact Lens Sensor

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Abstract

Background: Pilocarpine is cholinergic agent which acts as a direct muscarinic agonist of the ciliary muscles. It is one of the oldest glaucoma medications but at present, no data are available of its nocturnal effects on intraocular pressure (IOP). This report describes a case of progressive primary open-angle glaucoma (POAG) with nocturnal IOP spikes, where a 24-hour contact lens sensor (CLS) was used before and after the introduction of bedtime pilocarpine.

Case Presentation: We describe the case of a 66-year-old phakic female patient with a long-standing history of advanced POAG. Visual field mean deviation (MD) and retinal nerve fibre layer (RNFL) thickness showed clear disease progression despite persistent in-clinic IOP well within her established target range (< 15 mmHg) on once-daily latanoprost. Both OCT and gonioscopic examination confirmed an open angle. A 24- hour IOP-related monitoring with the CLS was scheduled and confirmed the relative diurnal stability of pressure levels, but showed a marked increase in signal throughout the night and coinciding with the time of sleep (10:00 pm) despite the instillation of latanoprost. Based on this finding, a therapeutic trial of once-daily pilocarpine 2% at bed-time was initiated. After one month, a new 24-hour CLS recording showed similar daytime levels to the previous one, but a considerably more stable recording following the application of pilocarpine drops (9:30 pm) and throughout the nocturnal period. Another recording after 6 months confirmed these findings.

Discussions: This report suggests that once-daily topical pilocarpine may have a nocturnal IOP-lowering effect, as an adjunct to prostaglandin agonists. Furthermore, we believe that once-daily 2% pilocarpine may be a good adjunct in glaucoma patients presenting elevated nocturnal IOP, particularly since common pilocarpine-related adverse events (e.g. brow ache, induced myopia) may be significantly reduced or become less relevant during the sleep period. A prospective study would be necessary to generalise this observation.

Keywords: *Glaucoma; Open-Angle; Prostaglandin; Adjunction; Combination; Sleep; IOP; CLS; Telemetry; 24h*

Background

Intraocular pressure (IOP) is the only modifiable risk factor for irreversible optic nerve damage in glaucoma [1]. Prostaglandin analogues (PGAs) are the most effective medication class for lowering IOP [2]. In recent years, increased attention has been directed to the circadian effects of glaucoma medications. While PGAs and, to a lesser degree, carbonic anhydrase inhibitors (CAI) have been shown to have a sustained IOP-lowering effect at night-time, beta-blockers and alpha-sympathomimetics do not [3-5].

Pilocarpine is cholinergic agent which acts as a direct muscarinic agonist of the ciliary muscles. It is one of the oldest glaucoma medications but has been largely abandoned for glaucoma therapy due to its unfavourable safety profile, the necessity of four times daily applications and modest efficacy [6]. At present, no data are available of its nocturnal effects on IOP.

The SENSIMED Triggerfish® contact lens sensor (CLS; Sensimed AG, Switzerland) is the only commercially available technology to measure 24-hour IOP-related patterns in an ambulatory setting [7,8]. The CLS measures limbal strain, changes of which are assumed to reflect a composite of intraocular pressure, intraocular volume, and biomechanical properties of the eye [9,10]. Previous studies evaluating the CLS have found good association with the circadian IOP profile [11-13] and have demonstrated its potency to detect medication-induced changes of IOP [14].

This report describes a case of progressive primary open-angle glaucoma (POAG) with nocturnal IOP spikes, where a CLS was used before and after the introduction of bedtime pilocarpine.

Case Presentation

We describe the case of a 66-year-old phakic female patient, who attended a large tertiary glaucoma center for the follow-up of a long-standing advanced POAG. Visual field mean deviation (MD) and retinal nerve fibre layer (RNFL) thickness showed clear disease progression despite persistent in-clinic IOP well within her established target range (< 15 mmHg) on once-daily latanoprost (Pfizer Inc., USA). Her most recent MD had progressed to -16.8 dBs in the right eye and -14.6 dBs in the left eye from -15.8 and -13.0 dBs respectively two years before (Figure 1). Mean RNFL were 42 µm and 65 µm in the right and the left eye respectively (Figure 2). Central corneal thicknesses were 531 and 532 µm and best corrected visual acuities (BCVA) were 0.9 and 0.8 (decimal) for the right (OD) and the left eye (OS) respectively. Biomicroscopic examination of the anterior chamber was entirely unremarkable and both optical coherence tomography (OCT) and gonioscopic examination confirmed an open angle, with all angle structures visible on 360°.

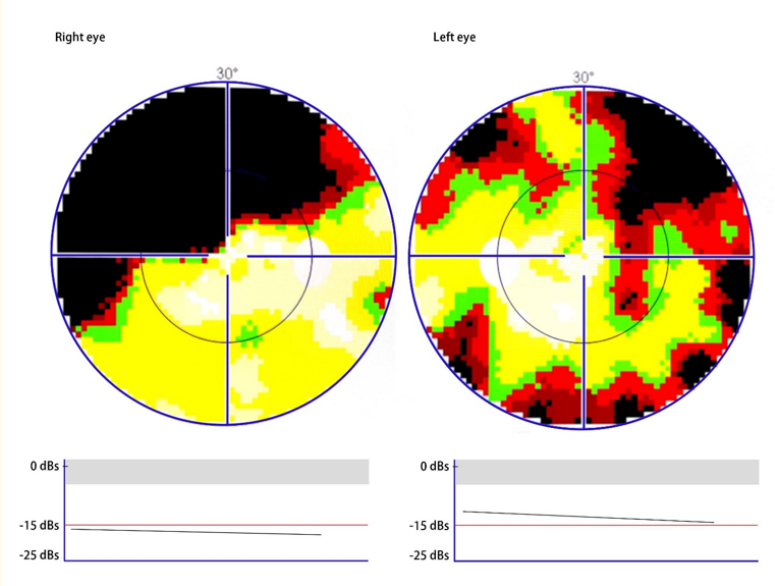

Figure 1: *Visual fields (top) showing a dense superior scotoma in the right eye (mean deviation -16.8 dBs) and a supero-temporal scotoma in the left eye (mean deviation -14.6 dBs). The progression graph (bottom) shows the progression in mean deviation over the last 24 months.*

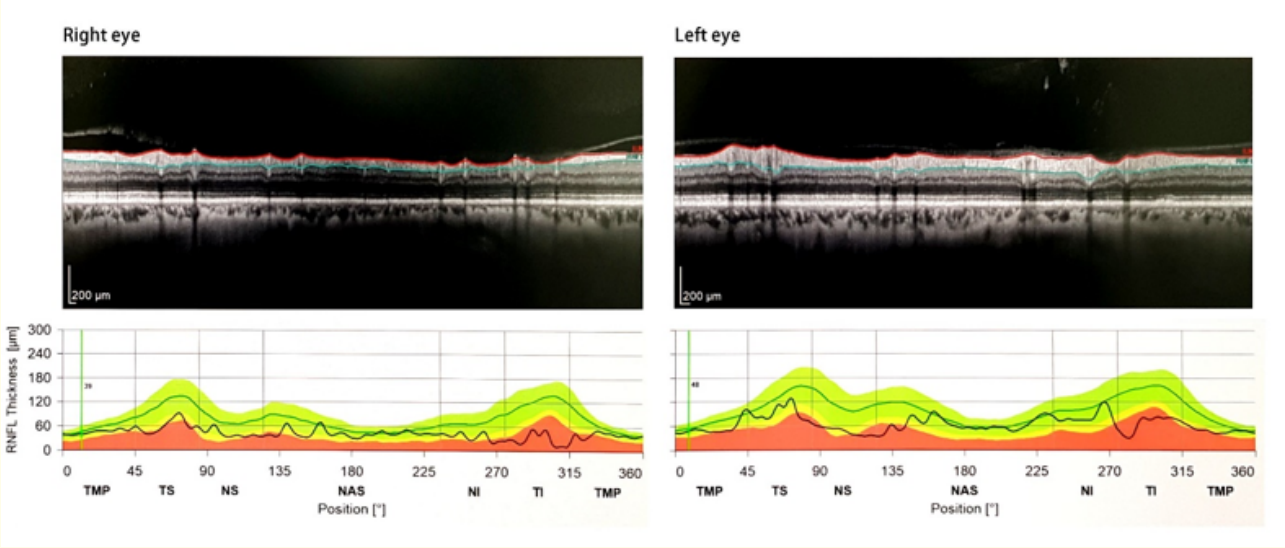

Figure 2: *Optical coherence tomography showing marked temporal inferior thinning of the retinal nerve fiber layer in the right eye and both superior and temporal inferior thinning in the left eye.*

Aside from a past medical history of atrial fibrillation, the patient was healthy and no other comorbidities or relevant family history.

Due to the uncontrolled nature of her disease, a 24-hour IOP-related monitoring of OD with the CLS was scheduled. The starting IOP measured by Goldmann applanation tonometry (GAT) before the start of the recording was 15 mmHg. The IOP-related profile confirmed the relative diurnal stability of pressure levels but showed a marked increase in signal throughout the night, and coinciding with the time of sleep (10 pm) despite the instillation of latanoprost (Figure 3, blue line).

Based on this finding, a therapeutic trial of once-daily pilocarpine 2% was initiated. The patient was advised to instil the pilocarpine drops 30 minutes after application of latanoprost and immediately before bedtime. After one month, the patient did not report any side effect or discomfort, and a new CLS recording was performed. GAT IOP were 11 and 13 mmHg at the start and at the end of the recording, respectively. The patient had been requested to follow a similar schedule to that of her first recording session. The new CLS recording (Figure 3, yellow line) showed similar daytime levels to the previous one, but a considerably more stable recording following the application of pilocarpine drops (21:30) and throughout the nocturnal period. Consequently, the patient was advised to continue once-daily latanoprost and pilocarpine treatment.

After 6 months, the patient was scheduled for a comprehensive ophthalmological examination with a repeat CLS recording. Structural and functional testing confirmed the absence of further glaucoma progression. GAT IOP were 10 and 12 mmHg at the start and at the end of the recording, respectively. The third CLS curve was largely comparable to the previous ones in its daytime patterns. The pronounced reduction of the nocturnal curve at 1 month, however, was not observed at 6 months, and the IOP-related profile showed a modest nocturnal rise (Figure 3, green line). The flattening of the nocturnal IOP-related curve was demonstrated by a significant reduction of the nocturnal area under the curve (AUC) of the CLS signal, which decreased from 104.1 (visit 1) to 10.1 (visit 2) and 50.1 (visit 3) (Holm-Bonferroni adjusted P-value < 0.001 based on repeated measure analysis of variance [ANOVA]), and an overall reduction of the CLS 24-hour amplitude (596.7, 305.9, 419.9 a.u. respectively). Two years after the introduction of the pilocarpine treatment, the patient's visual field and RNFL remained stable (MD -14.7 dBs and 43 µm respectively) and no adverse effect were reported.

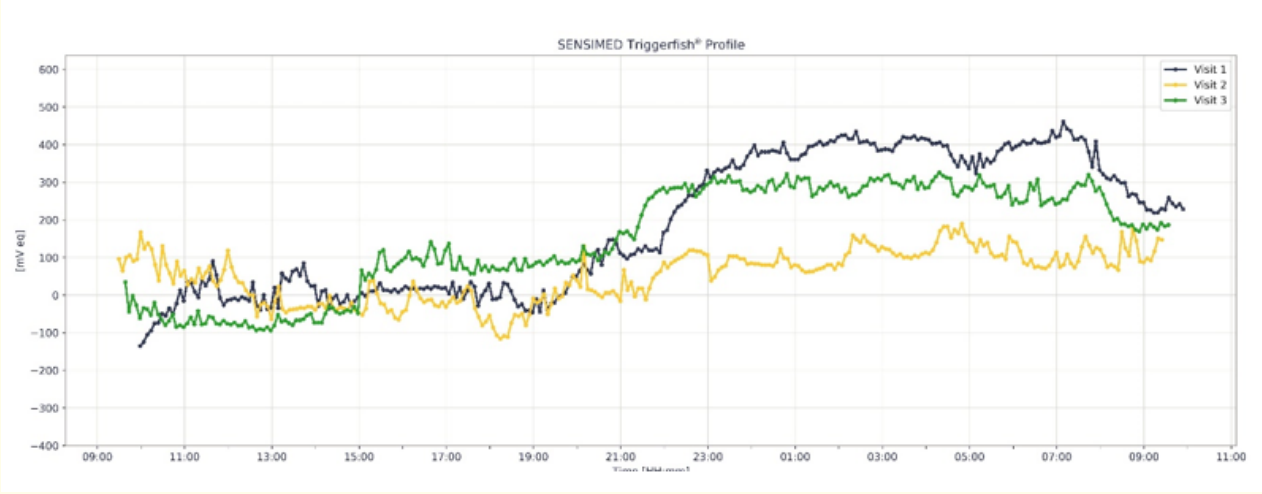

Figure 3: *Contact lens sensor output from 3 different recording sessions, showing intraocular pressure-related profiles (blue: first visit [baseline]; yellow: second visit [1 month]; green: third visit [6 months]). At each visit, eyedrops were applied right before sleep, between 21:30 and 22:00.*

Discussion

To the best of our knowledge, this is the first report evaluating the nocturnal IOP effects of adjunctive pilocarpine using continuous IOP-related monitoring with a CLS. In this atypical POAG patient who presented nocturnal IOP-related profile elevation, we observed a clear normalisation of the nocturnal profile following the bedtime instillation of pilocarpine 2%, associated with topical PGA, suggesting night-time IOP reduction. This effect was reproduced in the same eye, albeit to a lesser degree, six months after introduction. It is still unsure whether the finding of a reduced pilocarpine effect may be due to tachyphylaxis or inadequate adherence with the eyedrops over time.

Seibold et al. studied the effect of prostaglandin analog monotherapy, and showed a significant diurnal and nocturnal IOP-lowering effect associated with a significant reduction in blood pressure during night-time only [15]. At present, it is not known whether nocturnal IOP-lowering has the same protective effect on glaucoma development or progression as the widely studied daytime IOP reduction. It is, however, widely assumed that obtaining consistent IOP reduction throughout the 24-hour period is of benefit in glaucoma management. Indirectly, this hypothesis is supported by animal data of deleterious effects of dark-phase IOP [16] as well as the ability of successful glaucoma surgery to flatten the 24-h IOP curve [17] and reduce disease progression [18]. Furthermore, in a study of the CLS recordings from 445 open-angle glaucoma eyes, De Moraes., *et al*. demonstrated that nocturnal CLS signal parameters were directly associated with rapid deterioration of visual fields MD [19]. This further suggests the importance of monitoring and controlling night-time IOP. It will be, however, crucial to determine whether the associated systemic antihypertensive effect of topical pilocarpine analogs may have a detrimental effect on ocular perfusion pressure.

Our interest for the additivity of pilocarpine to PGAs stems from the fact that nocturnal effects of other available IOP-lowering medications were shown to be small-to-modest at best [20-23]. Yet, the increasing availability of 24-h IOP monitoring provides clinicians with the data on nocturnal IOP patterns, which often demonstrate elevated nocturnal IOP levels in treated glaucoma patients, thus the need for

adjunctive options to cover night-time elevations in IOP. Yamagishi-Kimura., *et al*. studied the combination of pilocarpine with Ripasudil, a rho kinase inhibitor, and found some degree of interreference between these two drugs [24]. This led to the clear recommendation to consider potential interreferences with other topical medications when introducing pilocarpine as an adjuvant. We believe that once-daily 2% pilocarpine may be a good adjunct in glaucoma patients with elevated nocturnal IOP, particularly since common pilocarpine-related adverse events (e.g. brow ache, induced myopia) may be significantly reduced or become less relevant during the sleep period, but a prospective study would be necessary to generalise this observation.

Conclusion

In conclusion, this report suggests that once-daily topical pilocarpine could have a nocturnal IOP-lowering effect, as an adjunct to PGAs in patients with elevated nocturnal IOP. More research is required to confirm our finding.

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Disclosure

Mansouri K: Santen (C), Sensimed (C), Topcon (S), Alcon (S), Allergan (S), Optovue (S); ImplanData (C); others: none.

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