The Efficacy of Unoprostone Isopropyl as an Adjunct to Topical β-blocker in Patients with Open Angle Glaucoma: A-6-Month Study

Yupin Leelachaikul MD*,
Ataya Euswas MD*

** Department of Ophthalmology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University*

Objectives: *To assess the efficacy and safety of unoprostone isopropyl as an adjunctive treatment to topical β-blocker in patients with primary open angle glaucoma (POAG).*
Study design: *This was a prospective, open-label clinical study.*
Material and Method: *A total of 44 eyes of 22 eligible patients whose intraocular pressure (IOP) was inadequately controlled by topical β-blocker were enrolled. Inclusion criteria consisted of patients with primary open angle glaucoma who either had IOP measurements ≥ 22 mmHg while on topical β-blocker monotherapy or had IOP measurements ≥ 18 mmHg while on dual therapy (topical β-blocker and a second drug of a different class which was to be discontinued prior to the study to allow washing out of its effects).*
Intervention: *Baseline IOP, pupil size, blood pressure and pulse rate were initially measured; the patients were then examined at 2nd, 4th, 8th, 12th, 18th and 24th weeks of following commencement of topical unoprostone isopropyl therapy (given twice daily).*
Main outcome measures: *IOP, pupil size, blood pressure and pulse rate were measured and were compared to baseline values.*
Results: *In 44 eyes of 22 eligible patients, unoprostone isopropyl resulted in a statistically significant IOP reduction of 24.6% ($p < 0.02$). The mean systolic blood pressure decreased from 132.79 ± 22.11 mmHg (range 100-180 mmHg) at baseline to 125.77 ± 18.40 mmHg (range 80-160 mmHg) at 24th week after unoprostone isopropyl administration. This reduction was statistically significant ($p = 0.002$) but was unlikely to have clinical importance. Both mean diastolic blood pressure ($p = 0.344$), pulse rate ($p = 0.306$), and pupil diameter ($p = 0.107$) were not significantly affected.*
Conclusion: *Topical unoprostone isopropyl beneficially provides additive IOP lowering effect to topical β-blocker in patients with primary open angle glaucoma. No serious systemic side effects were found in the present study.*

Keywords: *Unoprostone isopropyl, β-blocker, Primary open angle glaucoma, Intraocular pressure*

J Med Assoc Thai 2005; 88 (Suppl 9): S100-4
Full text. e-Journal: *http://www.medassocthai.org/journal*

Primary open angle glaucoma is the most common form of glaucoma although it is difficult to precisely establish the ratio of individuals with this disorder to the total number of patients with all forms of glaucoma. The epidemiologies will obviously be influenced by the population being studied, as well as the methods and criteria used to identify patients with glaucoma[1,2]. These patients frequently need more than one anti-glaucoma drug to control the progression of their disease and therefore, determination of the ideal pair or combination of drugs is needed. There are many groups of anti-glaucoma drugs such as β-adrenergic blocking agents, nonselective α-adrenergic agonists, selective α2-agonists, cholinergic drugs, carbonic anhydrase inhibitors and prostaglandin derivatives. Each group has distinct side effects and contraindications.

Correspondence to: Leelachaikul Y, Department of Ophthalmology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok 10400, Thailand. Phone: 0-2201-1560, E-mail: rapll@mucc.mahidol.ac.th

Unoprostone isopropyl (UF-021) is a prostaglandin derivative of PGF-2α. It is effective as monotherapy in intraocular pressure lowering in open angle glaucoma patients and its hypotensive effect is an increase of uveoscleral outflow without decreasing aqueous humor production which is different from β-adrenergic blocking agents[3]. Previous studies showed that there was statistically significant synergistic effect between β-adrenergic blocking agents and unoprostone isopropyl in open angle glaucoma patients[3,4]. The purpose of the present study was to investigate the efficacy and safety of unoprostone isopropyl as an adjunct to topical β-blocker in Thai POAG patients.

Material and Method

The present study was approved by Ramathibodi Hospital institutional review board. This was a prospective open-label clinical study in the patients from January 1, 2001 to December 31, 2002 at the out-patient clinic, Department of Ophthalmology, Ramathibodi Hospital, Mahidol University. There were 44 eyes of 22 patients enrolled by using the inclusion criteria i.e. POAG patients of either sex, who were at least 18 years old whose IOP was inadequately controlled while on ocular hypotensive monotherapy (IOP $\geq$ 22 mmHg) or whose IOP $\geq$ 18 mmHg while on dual ocular hypotensive therapy (topical β-blocker and another different drug group). Patients were excluded from the present study if they had narrow angle by gonioscopy, history of laser or other intraocular surgery within the past 3 months, previous ocular inflammation or infection within 3 months prior to the present study, current history of contact lens use or had a history of known allergy or sensitivity to unoprostone isopropyl or its components. The authors also excluded female patients who were pregnant or planning to become pregnant or were on a nursing period.

At baseline visit, all patients fulfilling all entry criteria had the following data recorded: best corrected visual acuity (BCVA), complete slit lamp biomicroscopy and gonioscopy (by YL), IOP measurement at 9 am and 3 pm (by Goldmann applanation tonometry), pupil size measurement, baseline automated perimetry (Humphrey 30-2 program), stereoscopic fundoscopy, blood pressure (BP), pulse rate (PR), and documentation of any concomitant diseases and medications.

In the eligible patient whose IOP was being treated with dual therapy, an appropriated washout period was allowed for discontinuance of the second adjunctive medication. The washout period was a minimum of 5 days to 4 weeks depending on the drug used. The medication schedule was β-blocker being instilled at 7 am and 7 pm and unoprostone isopropyl being instilled at 7.15 am and 7.15 pm.

The follow-up schedules were 2nd, 4th, 8th, 12th, 18th and 24th weeks. At each follow-up visit, clinical evaluation and IOP measurement were performed by the same investigator throughout the study and the data recorded include subjective symptoms, blood pressure and pulse rate, BCVA, pupil size, biomicroscopy, IOP measurements (at 9 am at all visits and at 3 pm at the 24th week visit).

Statistical Analysis

The descriptive statistics: range, mean, standard deviation (SD) were to present the results. The differences in mean IOP between baseline and the follow-up visits were analyzed by program n-Query Pair t-test (one side) of difference of means. P value less than 0.05 was considered significant.

Results

All 22 enrolled patients was followed-up until completion of the present study with no drop-outs. There were 10 men and 12 women; mean age of patients was 58.97 years of age (SD = 14.47, range 20-86 years old).

The authors found that unoprostone isopropyl addition resulted in a statistically significant IOP reduction of 24.6% ($p < 0.02$) at 9 am of the 24th week visit compared to the corresponding baseline (Table 1).

There was statistically significant reduction of systolic blood pressure ($p = 0.002$) but no significant changes in diastolic blood pressure, pulse rate, and pupil size after adjunctive therapy with unoprostone isopropyl (Tables 2-4).

The most common side effects were burning sensation and occurrence of superficial punctate keratitis (SPK) respectively which was mild and tolerable by the patients so that there was no drop-out due to adverse effects of the studied drugs (Table 5). The disappearance of SPK was shown after discontinuation of either drug at the end of the study.

Discussion

Effective management of glaucoma requires reduction of intraocular pressure (IOP)[5-9], typically achieved with medication, laser, or surgery. The standard approach for medication is to start with a single agent as monotherapy. A commonly used class of medications for this purpose in a cost-conscious health situation in developing countries i.e. the β-adrenergic

Table 1. IOP before and after adding unoprostone isopropyl (N = 44)

Time	Minimum IOP (mmHg)	Maximum IOP (mmHg)	Mean IOP (mmHg)	SD
Baseline 9 am	20	26	23.08	1.57
Baseline 3 pm	19	30	22.38	2.07
2nd week	15	20	17.41	2.52
4th week	14	22	17.12	3.20
8th week	14	22	16.67	3.07
12th week	13	20	16.47	2.88
18th week	12	20	17.32	2.90
24th week, 9 am	14	22	17.40	1.99
24th week, 3 pm	14	20	17.15	2.22

Table 2. The effect of unoprostone isopropyl on systolic (SBP) and diastolic blood pressure (DBP) (mmHg) (N = 22)

Blood pressure	Minimum	Maximum	Mean	SD	p-value
SBP at baseline	100	180	132.79	22.11	0.002
SBP at 24th week	80	160	125.77	18.40	
DBP at baseline	60	130	81.19	13.34	0.344
DBP at 24th week	60	130	80.36	11.18	

Table 3. The effect of unoprostone isopropyl on pulse rate (beats per min) (N = 44)

Pulse rate	Minimum	Maximum	Mean	SD	p-value
At baseline	58	96	69.34	8.49	0.306
At 24th week	60	86	71.52	7.93	

Table 4. The effect of unoprostone isopropyl on pupil size (mm) (N = 44)

Pupil size	Minimum	Maximum	Mean	SD	p-value
At baseline	1.50	4.00	3.01	0.61	0.107
At 24th week	1.50	4.00	3.08	0.51	

Table 5. Common side effects found in this study (N = 44)

Side effects	N (Percent)
Burning sensation	5 (11.4)
Superficial punctate keratitis (SPK)	4 (9.1)
Temporarily blurred vision	2 (4.5)
Red eye	2 (4.5)
Intraocular inflammation	0
Iris color change	0

blocking agents, can reduce IOP up to 20%. Although efficacious, a single agent may not provide adequate pressure reduction. In such a circumstance, other classes of medication will often be used with the hope that a better IOP-lowering effect can be obtained.

Unoprostone isopropyl lowers IOP primarily by increasing uveoscleral outflow without significant effect to aqueous humor production[3]. The β-adrenergic blocking agents lower IOP by decreasing the aqueous production. The clinically proven data from

previous studies[3,4] showed a favorable synergistic effect between this pair of anti-glaucoma medications.

The data from the present study showed that unoprostone isopropyl twice daily is effective in intraocular pressure reduction in POAG patients who previously instilled topical β-blocker and their intraocular pressure was not adequately controlled and the magnitude of the IOP reduction is comparable to that of the previous study[4,12]. The reduction was maintained during 6 months of the present study.

The present study showed the statistically significant reduction in systolic blood pressure but this was unlikely to be clinically important because of its very small magnitude. This finding may be a result of the small number of patients enrolled. However, the diastolic blood pressure, pulse rate and pupil size showed no statistically significant change after unoprostone isopropyl use. The result supported the previous study of Kojima S et al[10] that there were no statistically significant changes in blood pressure and pulse rate after using this drug.

The most common side effect of this drug in the present study was stinging upon application. The SPK was mild, had no effect on the vision, and disappeared after discontinuation of either drug without any sequelae. There was no iris-color change, unlike that found in Latanoprost[11] which is another prostaglandin derivative. Previous study by Yamamoto T et al[12] in 1997 showed no iris-color change in a 52-month study but there was this change in a 60-month study in a unilaterally treated Japanese eyes[13]. This may be because the present study was not long enough to demonstrate the iris-color change.

In conclusion, unoprostone isopropyl as an adjunctive agent to topical β-blocker results in significant additional intraocular pressure reduction in POAG patients without any serious systemic and local side effects. A study with a longer follow-up period is warranted to assess long term efficacy and safety of this combined therapy.

References

1. Shiose Y, Kitazawa Y, Tsukahara S, Akamatsu T, Mizokami K, Futa R, et al. Epidemiology of glaucoma in Japan - a nationwide glaucoma survey. Jpn J Ophthalmol 1991; 35: 133-55.
2. Leske MC, Rosenthal J. Epidemiologic aspects of open-angle glaucoma. Am J Epidemiol 1979; 109: 250-72.
3. Haria M, Spencer CM. Unoprostone. Drugs-aging1996; 9: 213-20.
4. Nordmann JP, Rouland JF. A comparison of the intraocular pressure-lowering effect of 0.5% timolol maleate and the docosanoid derivative of a PGF2a metabolite, 0.12% unoprostone, in subjects with chronic open-angle glaucoma or ocular hypertension. Curr Med Res Opin1999; 15: 87-93.
5. Collaborative Normal-Tension Glaucoma Study Group. Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients with therapeutically reduced intraocular pressures. Am J Ophthalmol 1998; 126: 487-97.
6. Collaborative Normal-Tension Glaucoma Study Group. The effectiveness of intraocular pressure reduction in the treatment of normal-tension glaucoma. Am J Ophthalmol 1998; 126: 498-505.
7. The Advanced Glaucoma Intervention Study (AGIS). The relationship between control of intraocular pressure and visual field deterioration. The AGIS Investigators. Am J Ophthalmol 2000; 130: 429-40.
8. The Glaucoma Laser Trial (GLT) and glaucoma laser trial follow-up study: results. Glaucoma Laser Trial Research Group. Am J Ophthalmol 1995; 120: 718-31.
9. Heijl A, Leske MC, Bengtsson B, Hyman L, Hussein M. Reduction of intraocular pressure and glaucoma progression: results from the early manifest glaucoma trial. Arch Ophthalmol 2002; 120: 1268-79.
10. Kojima S, Sukiyama T, Azuma I, Konishi N, Fujii H. Effect of topically applied isopropyl unoprostone on microcirculation in the human ocular fundus evaluated with a laser speckle microcirculation analyzer. Nippon Ganka Gakkai Zasshi 1997; 101: 605-10.
11. Ritch R, Shields MB. The glaucomas. 2nd ed. St. Louis: Mosby, 1996: 1385-482.
12. Yamamoto T, Kitazawa Y, Azuma I, Masuda K. Clinical evaluation of UF-021. Surv Ophthalmol 1997; 41(Suppl 2): 99-103.
13. Yamamoto T, Kitazawa Y. Iris-color change developed after topical isopropyl unoprostone treatment. J Glaucoma 1997; 6: 430-2.

ประสิทธิภาพของ Unoprostone Isopropyl ที่เสริมฤทธิ์กับ β-blockerในผู้ป่วยต้อหินมุมเปิดเรื้อรัง: การศึกษา 6 เดือน

ยุพิน ลีละชัยกุล, อัทยา อยู่สวัสดิ์

การศึกษาผลของ unoprostone isopropyl ว่ามีฤทธิ์เสริมกับ β-blocker ที่ผู้ป่วยใช้อยู่ตัวเดียวหรือใช้ยาอยู่สองชนิดร่วมกัน ที่เป็น β-blocker และยาชนิดอื่น ในผู้ป่วยต้อหินมุมเปิดเรื้อรัง 44 ตา (22 คน) ที่มีความดันตา ≥ 22 มม.ปรอท (ใช้ยา β-blocker ชนิดเดียว) หรือความดันตา ≥ 18 มม.ปรอท (ใช้ยา 2 ชนิดร่วมกัน) พบว่าการให้ยา unoprostone isopropyl วันละ 2 ครั้ง ร่วมกับ β-blocker ตรวจติดตามผลที่ 2, 4, 8, 12, 18 และ 24 สัปดาห์ เปรียบเทียบความดันตา ขนาดรูม่านตา ความดันโลหิตและอัตราการเต้นของชีพจร กับก่อนการบริหารยา ทำให้ความดันตาลดลงอย่างมีนัยสำคัญคิดเป็นร้อยละ 24.6 ความดันโลหิตขณะหัวใจบีบตัวก็ลดลงอย่างมีนัยสำคัญ โดยความดันโลหิตลดลงจาก 132.79 ± 22.11 มม.ปรอท เป็น 125.77 ± 18.40 มม.ปรอท ส่วนความดันโลหิตในขณะหัวใจคลายตัว อัตราการเต้นของชีพจรและขนาดรูม่านตาไม่แตกต่างกัน