行政院國家科學委員會專題研究計劃成果報告

計畫名稱：（中、英文）
原發性隅角閉鎖性青光眼的研究
Study on Optic Nerve Atrophy in Primary Angle-closure Glaucoma

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摘　　要

本研究的目的為明瞭原發性隅角閉鎖性青光眼的現況，從流行病學上與隅角開放姓青光眼的比較，考慮現今臨床診斷的標準，包括視神經的變化，並提出一系統化的流行病學的步驟。另一方面，則由於國人罹患本病，雖然經雷射虹膜切除，仍繼續進行，引發視神經之萎縮，以及眼壓之增高，因此從事最近新藥之藥物治療追蹤一年，控制本症的經驗。本實驗仍針對26眼26名由於各種藥物仍眼壓控制不良、視神經繼續惡化病人一年之追蹤，需要手術之病人，使用新藥 Latanoprost 0.005%，改善上脈絡膜之途徑，排出房水，降低眼壓，獲得一年追蹤成功之實驗。

關鍵詞：原發性隅角閉鎖姓青光眼，流行病學，視神經變化，藥物

ABSTRACT

(I) Prevalence of PACG and its blindness are increasing from increasing world geriatric population, and socio-economic development. Current diagnostic criteria is introduced, emphasizing ocular image studies, by stereo photographic study of optic nerve, and A-scan ultrasonography. A screen procedure is proposed. The risk/benefit ratio is also emphasized for early treatment of PACG.

(II) In this study, we tested the effectiveness of latanoprost as an intraocular pressure (IOP) lowering agent in cases of residual PACG. Twenty-six eyes of 26 PACG patients with persistently elevated IOP after iridectomy, despite treatment with conventional IOP lowering drugs (beta blockers and pilocarpine) were included. Latanoprost 0.005%, one drop daily, was added adjunctively to all eyes. The IOP decreased by about 21% ($p < 0.005$) during the first 3 months, and showed a reduction of about 36% at the end of 1 year. At the 1-year follow up, the IOP was well controlled (below 20 mmHg) in all eyes. These findings show that, in combination with beta blockade and pilocarpine, latanoprost can ameliorate residual PACG.

Key words: PACG, prevalence, optic nerve atrophy, drugs

Ocular disorder is like other filed of medicine, there are difference incidences and severity in geographically different part of the world Therefore, I shall emphasis to discuss from the 3 view points of public health on Asian PACG prevalence, diagnostic criteria and propose a screening procedure of Asian PACG.

From the global point of view, population of blindness increase with aging, Johnson in 1998 considered glaucoma is the third most frequent cause of blindness.

However, as all of us know it well that the number one cause of blindness from cataract, can be rather easily to restore the vision, while glaucoma need early detection and adequate treatment for prevention of vision loss. Quigley, as a matter of fact, considered glaucoma is the second most frequent cause of blindness, and there shall be bilateral ----- million people of bilateral blindness by the year of 2000.

The world population was just 6 billion July this year. Quigley estimated there shall be about the same number of glaucoma between POAG & PACG. And most of the PACG shall concentrated in Asia, especially West side of Asians.

Alsbirk reported as early as 1978 that in global aspect, PACG is the most important glaucoma. And PACG population is apparently shall increase in Asian in the future because of socioeconomic development associated increase of geriatric population and medical progress of this region.

However, from public health glaucoma investigation, POAG is apparently much more well studied, when compared with PACG.

Started from early 1970, well planned epidemiological studies of POAG, has been done from Framinghan eye study, Baltimore eye study to recent Egna-Neumarket study.

Let's learn the POAG study experience. It is important to know there are half of glaucoma patients are unaware of own disorder in these studies, and the criteria for detection, in addition to intraocular pressure, other parameters are also important for POAG screening. The pitfall of PACG study is no definite standard criteria for PACG diagnostic or screen test, and there are more than half of PACG patients are symptomless, that we can expect unaware glaucoma patient shall be an important issue.

Even among ophthalmologist because PACG is usually consider manifest as acute attack, the symptomless PACG is neglected.

Now, let's review quickly the PACG in general. First of all, PACG has strong tendency of racial difference. Much higher prevalence in Eskimo, Mongolian and its descendent of Chinese. Others are like India, Vietnamese, and a small part of south Africa.

PACG occurred frequently in small than-average eye that, refractory manifestation is

hyperopic eye.

Such small eye is constitute from small cornea, shallow anterior chamber shorter axial length that, biometric measurement is important parameters.

Lowe Consider such parameters have their own hereditary transmission and introduce the idea of polygenetic concept.

Aging increase the incidence and reached the highest point for male at age 60 and for female at 62. In our study, two third of 300 consecutive case are chronic type without prominent symptom.

In another word, acute type is only one third of our case. Female was twice the number of male as mention already.

Even though the reported incidence among chronic type and acute type are different from different authors, the symptomless chronic type, just like POAG detection, is important because of its normal tension and normal disc appearance in early stage.

PACG, therefore, is just as important as PAOG as cause of blindness.

Next, I would like to discuss on the criteria of PACG diagnosis. Our current gold criteria proposed by Kronfeld in 1948 is elevation of IOP with simultaneous angle closure. However, from public health view points to prevent blindness, early detection and easy & safe laser procedure; this is about the time to reconsider a new criteria base on this golden criteria.

Our three hundred case study in 1992 indicate visual detoriation to less then 0.1 was 33% in acute attack eye at 3.8 years after the acute attack while only 16% of less than VA 0.1 in non attack fellow eye who receive laser iridectomy soon after the attack. It is apparent that we should detect them ahead of attack for prevention of vision detoriation.

For diagnosis of the PACG, Epstein in his 1997 edition of "Lecture note on Glaucoma", proposed that base on gonioscopic examination only is enough to diagnosis the closure glaucoma.

Even though, we quite agree the importance of gonioscopic examination, in addition to history taking, ocular routine examination, slit lamp examination including von Herrick role, and indirect or direct gonioscopic examination, we would like to propose to add some objective numerical data from biometric study, optic nerve study, dark room prone position test, and even visual field for final judgement.

Slit lamp examination according to the von Herrick rule, to look at peripheral cornea or just focus on central anterior chamber depth are important.

Repeated gonioscopy around all quadrants of angle is especially important for early

detection. In addition, we must repeated this examination regularly in suspicious case, because chamber angle increase its narrowing with advance of age.

Ocular biometry can offer important information because of the smaller than average eye of PACG.

The pioneer work of Lowe in 1977 indicated that PACG is very rare if anterior chamber depth or ACD is deeper than 2.5 mm by Hag Strat measurement, and more than 95% of PACG are less than 1.8 mm ACD.

Our study on acute glaucoma demonstrated that ACD less than 2.70 mm is the most sensitive (94%) and specific (94%) parameter to differentiate acute glaucoma from non-glaucoma. To be noticed that this data is by A-scan, which nowadays is very popular, but include the cornea thickness.

Base on such concept of short axial length and shallow ACD, Christensen report a formula to predict the acute glaucoma, even though Wilensky wonder it value.

We have also engaged in the study of optic nerve atrophy in PACG in the past few years. Optic nerve study is another important parameter for chronic type of PACG as well as for follow up study of acute type.

Such study include the nerve fiber study by stereophotography, early model of Topcon disc analyzer & Topss, or Optical Coherent Tomography. Study of area of intrapapillary and parapapillar disc change are also performed. Those studies also indicated the importance of optic nerve change as it is also correlated well with visual field change.

Prone position test was developed by Hyams and Galin tested prone position test and dark room test respectfully in 17 PACG case. When respectfully done, the positive can reach 90%. However, to save the testing time we performed, combine dark prone positive test in PACG patient after an iridectomy, reported in Arch of Ophthalmology in 1979. Modify method by sitting position with head down on the desk with gaggle in the corner of office is a simple easy office procedure. This three tests, A-scan biometry, fundus optic disc examination and combine dark prone position test, all can be easily perform in office and in screening outside of a hospital or medical center. Final diagnosis of PACG thus can be judged by the information of history taking, gonioscopic examination and these 3 tests.

The next issue is on PACG screening.

We Asian are shame because in western country, the POAG screen procedures are much well established.

However, when we look into their glaucoma screen from the aspect of PACG, their criteria are inadequate, and lack of a standard procedure base of current thinking of PACG.

It is just at the beginning era to set up a standard procedure.

First of all, we would like to propose the classification of PACG based on the practical public health view points, rather than scientific. Such classification, in addition to establish PACG of acute or chronic type, shall include potential PACG development. We propose to set a group of high risk PACG or PACG suspect based on the above mention tests parameters.

In the treatment of any disorder, or potential blindness, we should consider the "ratio of benefit and risk" of our patient.

As mention by Kupfer, in a well development society, probably laser iridotomy can performed only in very high risk disorder, while in under developed area a 5% low risk is enough to perform a safe and easily laser iridectomy procedure.

In the Egna Neumarket study, they need two positive parameter to classify as PACG, neglecting the importance of gonioscopy. Therefore, in the propose today, I would like emphasize the importance of gonioscopic finding, called as one A, which emphasized gonioscopic finding and one B, which include other parameter as the standard criteria for PACG diagnostic criteria.

Based on our King San screen experience, we also would like to proposed stepwise procedure, emphasize the objective data in screening station, and coordinate with hospital center for further scientific examination, such as image analysis by angle study of UBM or Scheimpflug video image, and optic nerve analyzers.

In conclusion, prevalence of PACG and its blindness are increasing from increasing world geriatric population, and socio-economic development. Current diagnostic criteria is introduced, emphasizing ocular image studies, especially A-scan ultrasonography. A screen procedure is proposed. The risk/benefit ratio is also emphasized for early treatment of PACG.

Efficacy of Latanoprost as an Adjunct to Medical Therapy for Residual Angle-closure Glaucoma after Iridectomy

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ABSTRACT

Residual primary angle-closure glaucoma (PACG) after iridectomy is an important issue among Asians, especially Chinese. In this study, we tested the effectiveness of latanoprost as an intraocular pressure (IOP) lowering agent in cases of residual PACG. Twenty-six eyes of 26 PACG patients with persistently elevated IOP after iridectomy, despite treatment with conventional IOP lowering drugs (beta blockers and pilocarpine) were included. Latanoprost 0.005% one drop daily was added adjunctively to all eyes. Measurement of IOP at baseline and after the start of treatment with latanoprost indicated a significant IOP reduction. The IOP decreased by about 21% ($p < 0.05$) during the first 3 months, and showed a reduction of about 36% at the end of 1 year. At the 1-year follow up, the IOP was well controlled (below 20 mmHg) in all eyes. These findings show that, in combination with beta blockade and pilocarpine, latanoprost can ameliorate residual PACG after iridectomy, and could potentially forestall the need for further therapeutic intervention.

INTRODUCTION

Topical application of latanoprost 0.005% has been shown to reduce IOP in patients with open angle glaucoma, normal tension glaucoma, and ocular hypertension (1-3), and has recently become well accepted as an effective, well tolerated medication for IOP control in patients with open angle glaucoma (1-4). Latanoprost, previously called PhXa41, is a prostaglandin $F_{2\alpha}$ analogue. It is different from traditional IOP-lowering drugs, which lower IOP via reduction of aqueous production or increased outflow at the trabecular meshwork. Rather, latanoprost reduces IOP by increasing uveoscleral outflow, even in normal healthy eyes (4).

The mechanism of IOP elevation in primary angle-closure glaucoma (PACG) involves various factors, and is different from that in open angle glaucoma (5,6). Thus, whether latanoprost would be effective in PACG is important. Residual glaucoma after iridectomy in PACG is a common entity among Asians, especially among those of Chinese descent living in China, Singapore, or Taiwan(7), and may necessitate further laser or surgical procedures. Therefore, medications that can lower the IOP in patients with residual PACG could be of great therapeutic importance. Thus, the purpose of the present study was to examine the effects of latanoprost on IOP in iridectomized eyes with residual glaucoma receiving conventional IOP-lowering medications.

MATERIALS AND METHODS

Twenty-six eyes of 26 PACG patients (8 men, 18 women), aged 66.4±8.8 years (range 51 to 83 years), were prospectively enrolled in this study. All patients had documented residual PACG glaucoma after iridectomy, with inadequate IOP control in at least in one eye despite conventional medical therapy. Thus, all enrolled eyes were candidates for further laser or filtering surgery. Because all of the eyes had critical IOP levels, the design of this study was open-label, with emphasis on IOP change. Informed consent was obtained from each patient.

The eye with the higher IOP from each patient was selected for this study; the right eye was selected if both eyes showed about the same IOP. All 26 eyes had undergone iridectomy by laser (23 eyes) or conventional surgery (3 eyes), and additional argon laser

peripheral iridoplasty had been performed in 19 eyes. Conventional medical treatment included beta blockade and pilocarpine drops in all 26 eyes, and oral carbonic anhydrase inhibitor in 14 eyes. However, no distinction was made among various beta blockers, miotics or carbonic anhydrase inhibitors. All such medications were used in each test eye for at least 1 month prior to the study. Adjunctive latanoprost 0.005% one drop was administered once a day at bedtime.

Baseline IOP was stable, and was measured three times, 1 to 2 weeks apart prior to the beginning of latanoprost medication. The IOP was then measured at 1 and 2 weeks and 1, 2, and 3 months after the start of latanoprost treatment, and every 2 months thereafter for 1 year. All IOP measurements were performed at about the same time of day. If the IOP was well controlled below 16 mmHg after 3 months of latanoprost medication, oral carbonic anhydrase inhibitor or pilocarpine was removed from the regimen in patients who had difficulty tolerating these agents.

Topical examination by slit lamp was performed to evaluate the anterior segment. Gonioscopy showed peripheral synechia of various degrees, mostly in upper quadrants.

The efficacy of latanoprost therapy was evaluated by comparing the baseline IOP and the IOP at various intervals after the start of treatment, by Student's paired-t test. P values below 0.05 were considered statistically significant.

RESULTS

All 26 PACG patients continued latanoprost treatment for at least 3 months, after which the number of eyes available for analysis decreased. At the 1-year follow-up examination, only 8 eyes (8 patients) were included for analysis.

The mean IOP of the 26 eyes at base line prior to the start of latanoprost treatment was 23.24±4.31 mmHg. The mean IOP had dropped significantly (by about 21%) by the end of the first week of treatment. The IOP appeared to remain stable at about 18.3 mmHg through the end of the first month, and then decreased gradually throughout the study period. At the end of the follow-up period, the IOP had decreased by about 36% from the baseline value. The IOP values during the study period and the IOP as a percentage of the baseline value are shown in table 1 and figure 1. The magnitude of changes in IOP from the baseline value were also calculated as shown in table 2. The decrease in the mean IOP ranged from about 4.8 mmHg at 1 week to about 8.9 mmHg at 1 year after latanoprost was added to the conventional regimens.

No patients dropped out from the study and all tolerated latanoprost well, with no apparent adverse effects. However, 12 eyes showed slight transient conjunctival injection that usually disappeared the next morning. No eyelash change or iris pigmentation was noted. After 3 months of latanoprost treatment, 10 patients with good IOP control were taken off oral diamox and three patients discontinued pilocarpine drops. The IOP remained well controlled in these patients for the rest of study period.

TABLE 1.
The IOP reduction after adjunct latanoprost medication

	Intraocular pressure (mmHg) of the patients										
Day	0	7	14	30	60	90	120	180	240	300	360
Patient no.	26	26	26	26	26	26	17	14	10	9	8
Mean IOP	23.24*	18.33*	18.37*	18.31*	17.30*	17.35*	16.88*	15.92*	16.00*	15.26*	14.96*
(SD)	(4.31)	(5.54)	(5.16)	(4.77)	(3.47)	(4.02)	(4.20)	(2.26)	(3.39)	(2.89)	(2.57)
IOP %	100.00	78.86	79.03	78.78	74.45	74.68	72.62	68.51	68.85	65.65	64.39

IOP = intraocular pressure; SD = standard deviation; IOP% = (mean IOP on each examining day/mean IOP on Day 0) x 100;
*statistically significant ($p<0.005$) compared with the mean IOP on Day 0

TABLE 2.
The IOP difference from baseline after adjunct latanoprost medication

	Difference of IOP (mmHg) from baseline										
Day	0	7	14	30	60	90	120	180	240	300	360
Patient number	26	26	26	26	26	26	17	14	10	9	8
Mean of ΔIOP	0.00	-4.91*	-4.82*	-4.93*	-5.94*	-5.88*	-5.70*	-5.43*	-8.01*	-8.33*	-8.91*
(SD of ΔIOP)	(0.00)	(3.16)	(2.78)	(3.36)	(3.29)	(3.25)	(3.03)	(2.29)	(4.09)	(6.03)	(5.87)

IOP = difference of IOP from baseline (Day 0); IOP = intraocular pressure; SD = standard deviation;
*statistically significant ($p<0.005$) compared with the mean IOP on Day 0

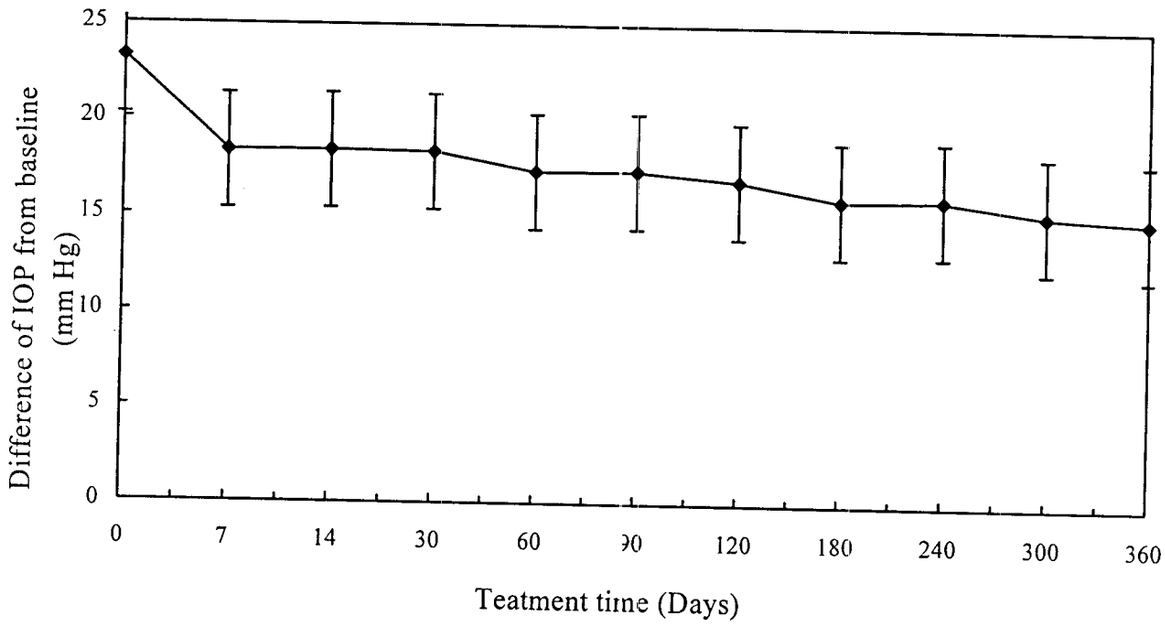

FIGURE 1. Reduction of IOP after Initiation of Adjunct Latanoprost Medication.

DISCUSSION

The mechanisms leading to PACG have been well documented and clarified in the past decade. The factors causing IOP elevation in PACG include pupillary block, lens factors, and angle iris crowding from plateau iris, quite different from those in open angle glaucoma (5,6,8).

PACG is a popular ocular disorder among Asians, especially Chinese. According to Quigley (9), PACG will account for half all glaucoma cases worldwide, around 30 million cases, by the year 2000. It is noteworthy that in Chinese, PACG is generally chronic, and residual chronic IOP elevation even after iridectomy is common. Lowe (7) reported that iridectomy alone may be insufficient to cure such residual glaucoma in Chinese, and that acute episodes of IOP elevation after iridectomy for PACG are familiar to ophthalmologists who treat Chinese patients.

The causes of IOP elevation in residual PACG from the pupillary block mechanism had been eliminated by iridectomy, and therefore only include angle crowding mechanisms and lens factors. In addition, damaged peripheral anterior synechia and trabecular function may also be involved (10). In cases of residual glaucoma, hypotensive medication may help avoid further laser or surgical procedures, if IOP can be well controlled.

In this report, all of our patients were already receiving at least two topical medications, including pilocarpine, which has proved to be effective for reducing IOP in patients with PACG (11). Our patients were therefore all candidates for further laser peripheral iridoplasty or surgical intervention. The addition of latanoprost 0.005%, however, reduced the IOP to below 20 mmHg soon after the start of treatment, rendering further invasive procedures unnecessary. The reduction in IOP (21% - 36% from baseline value) was statistically significant at all time points tested during the 1-year study period. Although pilocarpine might interfere with outflow through the suprachoroidal route in patients

receiving latanoprost, our observations revealed that combined medication with these two medications showed an additive effect. This finding is consistent with a previous report (12).

In summary, our findings indicate that latanoprost can effectively lower IOP in iridectomized patients with residual PACG receiving conventional medications, and therefore help avoid the need for further invasive procedures. Our long-term observations indicated that the IOP gradually decreased throughout the 1-year period of treatment. However, such gradual IOP lowering effect and whether the IOP can be maintained in a safe target range for longer periods require further study.

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Safety and Ocular Hypotensive Efficacy of A Single Dose of Metoclopramide or Droperidol in Healthy Subjects

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ABSTRACT

The purpose of this study was to evaluate the IOP lowering effect of two topical dopamine antagonists, metoclopramide or droperidol, in healthy subjects. Forty healthy volunteers were randomly assigned to receive, in double-masked fashion, topical administration of a single drop of 0.5% metoclopramide or 0.25% droperidol, with the fellow eye receiving isotonic saline as placebo. IOP was measured before and 1, 3, 5, and 7 hours after instillation of drugs. Ocular irritation and conjunctival congestion were also recorded at the time of each measurement.

In metoclopramide group, the maximal mean percentage change in IOP were -14.4% in tested eyes as compared with -10.8% in placebo-treated eyes 3 hours after instillation. And all the changes were not significantly different between metoclopramide-treated and placebo-treated eyes at all time points. In droperidol group, the maximal mean percentage change in IOP was -19.6% in tested eyes as compared with -17.7% in placebo-treated eyes at 3 hours after distillation. There were also no significantly difference between droperidol-treated and placebo-treated eyes. None of the volunteers reported ocular irritation or conjunctival congestion after instillation of the drugs.

In conclusion, while topical droperidol or metoclopramide tended to lower IOP in healthy subjects, the decrease in IOP did not differ significantly from that in placebo-treated eyes. Both drugs appear to be safe. Further studies with larger numbers of subjects at higher doses in glaucomatous subjects are needed before definite conclusions on drug efficacy can be drawn.

INTRODUCTION

Timolol , a β-adrenergic blocking agent widely used in the treatment of glaucoma, acts by inhibiting the formation of aqueous humor. There is an evidence showing that this reduction in aqueous humor formation might be caused by elimination of dopaminergic function in the eyes, resulting in decreased blood flow to the ciliary body, rather than by β-adrenergic blockade (1-3). In rabbits, elimination of dopaminergic function with reserpine has been shown to result in a decrease in intraocular pressure (IOP) that is reversed by dopamine(4). In one experiment, pretreatment with topical haloperidol in rabbits resulted in a further reduction in IOP to 46% of the baseline value (5). It was therefore postulated that dopamine antagonists might be useful for treating glaucoma , via reduction of aqueous humor formation and IOP. Furthermore, dopamine antagonists do not stimulate cholinergic receptors nor block β-adrenergic receptors, and therefore do not produce side effects produced by pilocarpine and timolol.

We conducted a randomized, double-masked, placebo controlled trial to determine the safety, ocular hypotensive effect, and the duration of action of a single drop of two topical dopamine antagonists, metoclopramide and droperidol, in healthy volunteers.

SUBJECTS AND METHODS

Forty healthy volunteers were recruited from National Taiwan University Hospital. Subjects with known ocular , systemic diseases or pregnancy were excluded from the study, as were those who were taking systemic β-adrenergic , dopamine receptor blocking agents or other systemic medications, or in whom ocular disease was detected at the time of initial examination. This study was approved by the Ethics Committee of National Taiwan University Hospital, and informed consent was obtained from all volunteers prior to participation. Subjects were randomly assigned to receive a single drop of topical application of either metoclopramide or droperidol in one eye, with the fellow eye serving as the control.

Intraocular pressure (IOP) was measured with a Goldmann applanation tonometer under topical anesthesia using 0.5% proparacaine hydrochloride (Alcaine, Alcon-Couvreur). IOP was measured 10 minutes before application of topical 0.5% metoclopramide or 0.25% droperidol, and 1, 3, 5,and 7 hours after the instillation of drugs. Eye drops containing either the tested drug or placebo (isotonic solution) were instilled independently by trained ophthalmic nurses in a double-masked fashion.

Visual acuity, brachial artery blood pressure, and pulse rate were measured at baseline, and at 1, 3, 5, and 7 hours after administration of topical metoclopramide or droperidol. A throughout slit-lamp examination was performed before each IOP measurement to determine iritis score and conjunctival injection scores (Table 1) as well as the corneal epithelial problem, and subjects were questioned about ocular symptoms such as ocular pain and irritation in systematic manor.

RESULTS

Twenty volunteers received topical 0.5% metoclopramide , while the others received 0.25% droperidol. The mean age of the volunteers was 25.8±1.8 years old, and male-female ratio was 3:1.

Topical metoclopramide produced a small reduction in IOP, with the maximum reduction of 14.4% from the baseline value occurring 3 hours after instillation; the mean reduction from baseline IOP in control eyes at 3 hours was 10.8%. There was no statistically significant difference in IOP reduction between the tested and control eyes at any of the time points (Table 2). The reduction in IOP produced by topical administration of 0.25% droperidol was greater than that produced by placebo only at 3 hours post-instillation, and this difference was not statistically significant either. At all other time points, the reduction was greater in eyes treated with placebo without significant difference
(Table 3).

TABLE 1
Description of Iritis and Conjunctival Injection Scores

Severity	Iritis score	Conjunctival injection score
0 = Normal	0 = < 5 cells(normal)	0 = Normal
1 = Mild	1 = 5-10 cells	1 = Slight congestion and dilation of limbal vessels
2 = Moderate	2 = 11-20 cells	2 = Marked congestion and dilation of limbal vessels
3 = Severe	3 > 20 cells	3 = Marked congestion and dilation of limbal vessels, hyperemia, excessive lacrimation and epiphora

* Severity applies to both iritis and conjunctival injection score.

TABLE 2

Mean (±Standard Deviation) Percentage Changes in IOP from Baseline Value after Instillation of Metoclopramide or Placebo in Healthy Volunteers

Treatment	1 hr	3 hr	5 hr	7 hr
M(20 eyes)	-2.7±12.6	-14.4±25.1	-8.72±15.1	-5.7±12.5
P(20 eyes)	-3.6±10.5	-10.8±27.9	-5.5±19.3	-8.0±17.2
p values	0.46	0.68	0.36	0.41

M: 0.5% Metoclopramide eye drop P: Placebo (isotonic solution)

TABLE 3

Mean (±Standard Deviation) Percentage Change in IOP from Baseline Value after Instillation of Droperidol or Placebo in Healthy Volunteers

Treatment	1 hr	3 hr	5 hr	7 hr
D(20 eyes)	-6.6±18.1	-19.6±25.0	-11.1±17.4	-4.2±12.4
P(20 eyes)	-7.9±12.6	-17.7±24.8	-16.0±13.4	-7.5±13.1
p values	0.15	0.84	0.42	0.76

D: 0.25% Droperidol eye drop P: Placebo (isotonic solution)

Neither topical metoclopramide nor droperidol caused ocular symptoms such as ocular pain or increased ocular irritation scores. Similarly, there were also no ocular signs such as increased conjunctival injection scores or ocular inflammation (iritis) scores .

There were no significant changes in systolic or diastolic blood pressure or pulse rate after topical administration of metoclopramide at any of the time points. In the droperidol group, there were also no significant changes in systolic pressure or pulse rate although the diastolic blood pressure decreased significantly from baseline at 1, 3 and 5 hours (-2.7 mmHg, -3.7 mmHg, -4.6 mmHg respectively). These changes were clinically negligible, even though they were statistically significant.

DISCUSSION

Previous studies in rabbits have shown an impressive reduction in IOP of up to 30% after topical administration of droperidol (6). It was therefore suggested that dopamine antagonists may be used as an effective antiglaucoma drug. Sheppard et al (1986) showed that oral haloperidol produced significant IOP reduction in non-glaucomatous volunteers at 3 and 4 hours after drug administration (7). Dopamine antagonists may therefore effectively reduce IOP in

humans. However, topical application of haloperidol in human volunteers in Lavin and Andrew's study (1% or 0.125% haloperidol) and Elibol et al's study (0.5% haloperidol) failed to exert a significant IOP reduction in non-glaucomatous volunteers (8,9). In our study, topical administration of 0.25% droperidol or 0.5% metoclopramide showed a slight IOP reduction tendency especially at 3 hours after topical application, although these reductions differed little from those in placebo- treated eyes.

Several factors may explain the discrepancy between our results and those from animal experiments. First , the penetration of corneal epithelium may be different in humans than in experimental animals, and the concentration of dopamine antagonists in the anterior chamber may also differ. Higher concentrations of topical drugs may increase the concentration in the aqueous humor, thereby increasing their effect. Further, it is possible that the laboratory animals and humans differ in their response to pharmacologic intervention in aqueous humor formation and outflow. Previous studies have shown that the effect of timolol is less prominent in experimental animals (10) than in human beings (11). Finally, it is possible that dopamine antagonists may have a greater effect on increasing aqueous humor outflow or reducing aqueous production in patients with glaucomatous conditions. Further studies should be performed on glaucomatous or ocular hypertensive patients to draw a definite conclusion.

In our study, neither topical metoclopramide nor droperidol resulted in any ocular pain, irritation, inflammation, or conjunctival injection. Nor did they produce any systemic side effects other than a minimal reduction in diastolic blood pressure change that was not clinically significant. It seems reasonable to conclude that droperidol and metoclopramide maybe safe for topical use. Further clinical trials with higher concentrations are needed to clarify the role of these two agents in the treatment of glaucoma.

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