Cardiovascular effects of timolol maleate, brimonidine or brimonidine/timolol maleate in concomitant therapy

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ABSTRACT.

Purpose: **To examine the influence on maximal exercise performance in young healthy volunteers of timolol 0.5%, brimonidine 0.2% or placebo *versus* brimonidine 0.2% and timolol 0.5% used concomitantly.**

Methods: **The subjects in this prospective, double-masked, crossover comparison were dosed 15 min prior to treadmill testing. A period of 1 week was allowed between tests.**

Results: **The 20 subjects who completed the trials (average age 24.5 ± 7.4) had a mean maximum exercise heart rate of 196 ± 12 bpm for placebo, 182 ± 13 bpm for timolol, 187 ± 10 bpm for brimonidine, and 186 ± 11 bpm for timolol/brimonidine concomitant therapy ($p < 0.005$). During recovery, the placebo group demonstrated a statistically higher systolic blood pressure (min 6) and pulse (mins 2 and 4) ($p < 0.01$). In addition, subjects treated with timolol/brimonidine demonstrated more premature contractions (atrial or ventricular) overall during exercise and recovery ($p = 0.01$). The brimonidine and concomitant treatment groups showed the greatest number of adverse events per subject, the most common of which were dizziness and fatigue ($p = 0.031$).**

Conclusion: **This study suggests that both timolol and brimonidine, used alone and concomitantly, cause cardiovascular effects consistent with their pharmacology.**

Key words: β-blockers – centrally acting α-adrenergic agonist – glaucoma – exercise – premature contractions

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Ophthalmologists must be familiar with the safety profile of the ever-increasing number of topical agents available to treat elevated intraocular pressure (IOP). However, little evaluation of systemic interactions associated with concomitant therapy has been carried out. This may be of particular significance when two agents from separate classes of medicines both demonstrate cardiovascular effects.

Two such classes of medicines are the centrally acting topical α_2-adrenergic agonists and the non-selective β-adrenergic blockers, both of which are commonly used in the treatment of glaucoma. Both of these classes demonstrate potentially similar pharmacological effects on the cardiovascular system, including decreased heart rate, inotropic action of the heart, cardiac conduction and blood pressure, but through different mechanisms. In addition, both classes of medicines could potentially increase peripheral vascular constriction (Williams et al. 1977; Reid 1986; Ding Xuan et al. 1998; Stewart & Castelli 1996; Azevedo et al. 1999). The labeling of brimonidine includes a caution against using the medicine with either ophthalmic or systemic β-blockers.

The primary objective of this trial was to determine the influence of timolol maleate 0.5%, brimonidine 0.2%, or placebo as monotherapy on the cardiovascular system, at rest and during maximal exercise performance, in healthy volunteers.

Materials and Methods

Subjects

Prospective participants in the trial were required to fulfil the following criteria: they were to be aged 18–45 years; they were to be willing to comply with the investigators' protocol and instructions; and they were to have excellent ocular and systemic health with no known pulmonary or cardiac disease.

A young population was chosen both because they represent a safer study group in evaluating the concomitant use of two medicines that might cause cardiac effects, and because they produce more uniform effort in treadmill testing than

an older age group. Subjects were excluded if they had any history of allergic hypersensitivity or poor tolerance to any components of the study medicines; if they were women of childbearing potential not using reliable birth control; if they were pregnant or lactating women; and if their history gave any contraindications to β-adrenergic blockers or α_2-adrenergic agonists.

Procedures

Subjects signed an Institutional Review Board (Pharmaceutical Research Corp., SC, USA) approved informed consent document before any procedures were performed. The screening visit (Visit 1) was held a maximum of 14 days prior to the active treatment visits. During this visit, examinations included a physical examination, resting blood pressure and pulse readings, electrocardiography, applanation tonometry, visual acuity and anterior segment and dilated ocular examinations.

Qualifying subjects were asked to return for the active treatment portion (Visits 2–4) of the trial. At the initial active treatment visit (Visit 2), subjects were randomized by Latin-square technique to one of four treatment groups, each of which represented two treatments. These included placebo/placebo (Hypotears™, Ciba Vision Ophthalmics, Atlanta, Georgia, USA), placebo/brimonidine 0.2% (Alphagan®, Allergan, Irvine, California, USA), placebo/timolol maleate 0.5% solution (Timoptic™, Merck, Blue Bell, Pennsylvania, USA) and brimonidine/timolol maleate. Each subject received one drop topically of each medicine in each eye, given 5 min apart. The second medication was given 15 min before the exercise test (Urtti et al. 1994). All subjects were dosed by the same unmasked study co-ordinator. All other staff members, the subject and the investigator were masked to the medication given. Maximum exercise testing was performed according to a modified Bruce (1971) protocol. Following the initial exercise test, subjects were instructed to return at 1 or 2 week intervals for subsequent treatments (Visits 3 and 4).

Statistics

All data testing was two-sided. The study had an 80% power to exclude a 6.0 bpm difference between groups (Internal data, Pharmaceutical Research Corporation). Primary and secondary safety variables were analysed by ANOVA. These variables included time to exhaustion, heart rate (apart from maximum exercise rate), blood pressure, EKG intervals and the number of adverse events per person among individual treatment groups. Analyses between individual treatment groups were performed with a paired *t*-test. When multiple ANOVA tests were used for a single parameter (i.e. exercise and recovery blood pressure or heart rate), p-levels were adjusted (0.05/4) according to Bonferroni. The incidence of atrial or ventricular premature contractions and the number of individuals among treatment groups with an adverse event were evaluated by a Chi-square test. (Book 1978)

Results

Subjects

We randomized 22 subjects for this trial (Table 1). During the trial, one subject was discontinued in period 1, as per protocol, due to a run of three atrial extrasystoles during exercise testing (timolol maleate treatment), and another was discontinued due to a sprained ankle between treatment periods.

Heart rate

Maximum heart rate was noted (Table 2) to be different among treatment groups, with the placebo-treated group showing the highest mean value ($p < 0.005$). Among individual active treatment groups, each medicine reduced heart rate significantly more at maximum exercise than did placebo ($p < 0.002$). During recovery, a significantly different heart rate was observed among treatment groups at 2 and 4 min, with all active treatment groups showing reduced heart rates compared to the placebo group ($p < 0.005$).

Blood pressure

No significant change in blood pressure was noted among treatment groups during exercise (Table 3). However, during recovery, all active treatment groups were observed to show a trend towards decreased systolic blood pressure at min 4 ($p = 0.015$) and a significant reduction at min 6 ($p = 0.009$), compared to subjects treated with placebo.

Electrocardiograph monitoring

A statistical difference between groups existed in the number of subjects demonstrating premature ventricular contractions during exercise ($p = 0.008$) (Table 4) and atrial premature contraction during recovery ($p = 0.010$). Both types of premature contractions were highest in the concomitant treatment group. Further, the overall incidence of atrial and ventricular premature contractions combined during exercise and recovery was higher in the concomitant treatment group than in the other three groups ($p = 0.001$).

A difference in the P-R cardiac interval during recovery was apparent between

Table 1. Patient characteristics. Mean and standard deviation.

Patients		
Age (years)	24.4 ± 7.4	
Gender		
	Female	16
	Male	4
Ethnicity		
	Asian	1
	White European	19
Exercise history		
	Performed routine exercise	13
	Performed no routine exercise	7
Systemic Disease (> 5% incidence)		
	Acne	4
	Seasonal allergies	3
Systemic medications: (> 5% incidence)		
Oral contraceptives	10	
Antibiotic	4	
OTC headache	4	
Anti-acne	4	
OTC sinus	2	
Loratadine	2	

OTC = over the counter

Table 2. Heart rate (beats per minute). Mean and standard deviation.

	Placebo ($n = 20$)	Timolol maleate ($n = 20$)	Brimonidine ($n = 20$)	Brimonidine/ timolol maleate ($n = 20$)	p-value
Exercise					
Initial heart rate	68.6 ± 15.6	66.0 ± 14.9	70.1 ± 15.3	70.8 ± 17.0	> 0.100
1 min	125.6 ± 17.8	119.3 ± 10.7	122.4 ± 16.0	119.2 ± 15.9	> 0.100
2 min	130.5 ± 18.5	127.3 ± 14.7	132.4 ± 18.1	125.2 ± 15.9	> 0.100
3 min	137.6 ± 18.9	133.8 ± 17.4	138.4 ± 20.2	131.2 ± 20.0	> 0.100
4 min	160.0 ± 18.1	156.2 ± 17.6	163.9 ± 19.61	154.4 ± 18.6	> 0.100
5 min	171.2 ± 18.7*	167.8 ± 16.8	171.3 ± 18.3	167.0 ± 19.3*	> 0.100
6 min	181.8 ± 15.5*	171.7 ± 12.5*	178.5 ± 14.7*	175.5 ± 13.5*	> 0.100
7 min	182.4 ± 12.7*	177.3 ± 12.6*	181.8 ± 14.9*	181.6 ± 11.6*	> 0.100
8 min	188.8 ± 7.8*	185.2 ± 12.0*	185.4 ± 13.7*	183.4 ± 9.4*	> 0.100
9 min	194.0 ± 8.5*	193.0 ± 24.0*	189.5 ± 14.8*	194.0 ± 8.5*	> 0.100
Maximum	195.5 ± 12.0	181.6 ± 12.8	187.4 ± 9.9	185.9 ± 11.1	< 0.005
Recovery					
Initial heart rate	155.6 ± 23.8	140.6 ± 16.6	159.2 ± 13.6	151.9 ± 20.6	> 0.100
2 min	119.1 ± 23.2	112.7 ± 8.0*	118.0 ± 9.6*	116.7 ± 15.9*	< 0.005
4 min	115.0 ± 8.8*	104.2 ± 3.5*	109.2 ± 10.5*	108.1 ± 9.6*	< 0.005
6 min	112.7 ± 10.5*	103.0 ± 3.0*	110.3 ± 7.9*	106.0 ± 6.9*	> 0.100

*n < 20 due to subject drop-out from having reached maximum exercise

Table 3. Blood pressure (mm Hg).

	Placebo ($n = 20$)	Timolol maleate ($n = 20$)	Brimonidine ($n = 20$)	Brimonidine/ timolol maleate ($n = 20$)	p-value
Exercise					
Initial systolic	112.2 ± 13.4	115.4 ± 14.4	115.4 ± 15.2	114.6 ± 12.9	> 0.100
2 min	126.2 ± 21.1	121.8 ± 16.9	124.8 ± 21.1	123.2 ± 16.3	> 0.100
4 min	136.6 ± 18.4	132.0 ± 12.5	134.6 ± 19.2	137.4 ± 12.9	> 0.100
6 min	149.4 ± 16.8**	146.4 ± 11.2*	148.6 ± 17.6*	152.2 ± 10.7*	> 0.100
Initial diastolic	66.6 ± 8.1	71.2 ± 10.2	71.3 ± 8.6	70.8 ± 9.0	> 0.100
2 min	68.8 ± 9.8	70.2 ± 10.3	70.6 ± 8.4	70.7 ± 9.4	> 0.100
4 min	74.5 ± 7.4*	73.5 ± 9.2	74.6 ± 9.1*	75.0 ± 6.3	> 0.100
6 min	74.4 ± 5.3*	78.6 ± 9.0*	76.7 ± 8.2*	76.0 ± 8.9*	> 0.100
Recovery					
Initial systolic	171.5 ± 22.9	170.8 ± 20.6	170.6 ± 19.6	171.0 ± 21.9	> 0.100
2 min	161.2 ± 22.8	156.9 ± 22.5*	158.9 ± 24.4*	161.7 ± 20.0*	> 0.100
4 min	148.2 ± 22.1*	140.4 ± 16.6*	140.6 ± 13.8*	139.8 ± 19.8*	= 0.015
6 min	136.7 ± 28.3*	128.6 ± 16.6*	123.3 ± 6.3*	128.0 ± 15.6*	= 0.009
Initial diastolic	70.2 ± 8.3	73.4 ± 8.5	69.3 ± 7.9	67.9 ± 8.0	> 0.100
2 min	65.1 ± 8.0	67.9 ± 7.6*	67.2 ± 9.6*	64.5 ± 7.3*	> 0.100
4 min	58.3 ± 7.2*	63.1 ± 7.9*	64.0 ± 6.8*	60.7 ± 5.1*	> 0.100
6 min	62.7 ± 11.5*	62.6 ± 10.3*	62.3 ± 6.1*	60.6 ± 4.8*	> 0.100

*n < 20 due to inability to hear Korotkoff sounds during run or reaching maximum exercise already

Table 4. Individuals with an atrial premature contraction (APC) and/or premature ventricular (PVC) contraction.

	Placebo ($n = 20$)	Timolol maleate ($n = 20$)	Brimonidine ($n = 20$)	Brimonidine/ timolol maleate ($n = 20$)	p-value
Exercise					
APC	5	6	4	6	= 0.85
PVC	11	2	6	12	= 0.008
Recovery					
APC	0	1	2	6	= 0.010
PVC	2	3	1	6	= 0.20
Total incidence	18	10	13	30	< 0.001

the treatment groups for those subjects who demonstrated premature contractions (atrial or ventricular) ($n = 10$, 16 s), as compared to the placebo group (0.14 s) ($p = 0.03$). Cardiac intervals were not measurable during exercise.

Adverse events

There was no statistical difference between groups regarding the number of subjects reporting adverse events after dosing ($p = 0.22$) (Table 5). There was a difference, however, in the mean number of total adverse events per subject in the brimonidine group (0.6) and the concomitant treatment group (0.6), compared to the placebo group (0.1) and the timolol maleate group (0.25) ($p = 0.031$). Typical symptoms following dosing were dizziness and fatigue.

Discussion

Systemic beta-adrenergic blockade activity is typically demonstrated clinically by a reduced maximum exercise heart rate, as shown by stress testing in healthy individuals (Reid 1986; Azevedo et al. 1999). Previous studies have shown that topical timolol consistently reduces maximum exercise testing in healthy subjects (Dickstein & Aarsland 1996; Stewart et al. 1999).

In contrast, systemic centrally acting α_2-adrenergic agonism is typically shown by symptoms of fatigue and by reduced blood pressure at rest (Azevedo et al. 1999). Fatigue has been noted to occur in as many as 10% of patients with primary open-angle glaucoma or ocular hypertension treated with brimonidine in the multicenter regulatory trials (Schuman 1996; Katz et al. 1999). Additionally, Nordlund, using a submaximal exercise test in healthy subjects, found reduced blood pressure at rest during the recovery period for brimonidine, consistent with its centrally acting activity, but not a reduction in exercise heart rate (Nordlund et al. 1995).

The primary objective of this trial was to determine the influence on the cardiovascular system of timolol maleate 0.5%, brimonidine 0.2%, or placebo as monotherapy *versus* brimonidine 0.2% and timolol maleate 0.5% used together, in healthy volunteers, at rest and at maximal exercise performance.

The study found that treatment with timolol maleate resulted in the expected reduction in heart rate, with maximum exercise testing consistent with systemic β-adrenergic blockade. In a similar fashion, treatment with brimonidine brought about reduced blood pressure and heart rate during recovery and at rest, consistent with centrally acting α_2 agonism. Compared to placebo, brimonidine also reduced heart rate on maximum exercise testing and during recovery. This finding is also consistent with centrally acting α_2 agonism. Nordlund's study used a submaximal test, by which no reduction in heart rate from placebo was found. However, in our study the differences on heart rate brought about by placebo with brimonidine only became evident towards maximum exercise effort.

The use of concomitant timolol maleate and brimonidine, given as separate agents, did not alter heart rate or blood pressure beyond the levels produced by each of the agents used as monotherapy. However, statistical differences in the number of subjects demonstrating ventricular premature contractions existed between treatment groups during exercise, and in the number of subjects demonstrating atrial premature contractions during recovery. Overall, the concomitant use of brimonidine and timolol maleate demonstrated the greatest incidence of atrial and ventricular premature contractions during both exercise and recovery.

The existence in the healthy population of atrial and ventricular premature contractions is generally thought to be benign (Beers & Berkow 1999). However, in patients with known heart disease, premature ventricular contractions increase the incidence of sudden death, presumably due to ventricular tachycardia (Goldstein et al. 1996). Atrial premature contractions in cardiac patients are also thought to be benign, unless they acutely follow myocardial infarction, when they may also lead to sudden death (Beers & Berkow 1999). A significant increase in the P-R interval (atrial conduction time) was evident in all active treatment groups in subjects having a premature contraction during recovery, and could potentially have contributed to an escape phenomenon.

An increase in the mean number of adverse effects per individual was observed in the brimonidine therapy group and in the brimonidine/timolol maleate concomitant therapy group ($n = 12$ each), compared to the placebo group ($n = 2$) ($p = 0.031$). Most symptoms resulted from fatigue and dizziness, consistent with centrally acting α_2-agonist or β-blockade therapy.

This study suggests that both timolol maleate and brimonidine cause systemic cardiovascular effects and symptoms consistent with their pharmacology. The concomitant use of these medicines may increase premature contractions during and following exercise.

The current study evaluated pharmacological effects on young healthy individuals without the target disease indicated for the study medicines. Consequently, care must be taken when applying the results to glaucoma patients, who, typically, are older and may or may not have cardiovascular disease. Importantly, in predisposed individuals, β-receptor blockade has previously been shown to potentially precipitate or worsen cardiac block, or aggravate decompensated heart failure (Stewart & Castelli 1996; Stewart et al. 1999). However, apart from a small reduction in blood pressure, clinically significant cardiac effects in a glaucoma population from brimonidine alone, or from a combination of timolol

Table 5. Adverse events following dosing, exercise and recovery.

	Placebo ($n = 20$)	Timolol maleate ($n = 20$)	Brimonidine ($n = 20$)	Brimonidine/ timolol maleate ($n = 20$)
Fatigue	1	0	1	2
Dizziness	1	2	4	3
Calf cramping	0	1	1	1
Ocular fatigue	0	1	1	2
Ocular dryness	0	1	1	0
Heart palpitations	0	0	1	0
Nasal irritation	0	0	1	2
Blurry vision	0	0	1	0
Dry mouth	0	0	1	0
Headache	0	0	0	1
Slurred speech	0	0	0	1
Total events	2	5	12	12

and brimonidine, have not been demonstrated and remain an area for further research. (Derick et al. 1997; Chen et al.; 2001)

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