Assessment of bronchial effects following topical administration of butylamino-phenoxy-propanol-acetate, an oculoselective β -adrenoceptor blocker in asthmatic subjects

K. G. BAUER¹, F. BRUNNER-FERBER³, L. M. DISTLERATH³, E. A. LIPPA³, B. BINKOWITZ³, P. TILL² & G. A. KAIK¹

University of Vienna Medical School, ¹Division of Internal Medicine I, Clinical Pharmacology Unit, and ²Division of Ophthalmology II, Vienna, Austria, and ³Merck Sharp & Dohme Research Laboratories, Rahway, New Jersey, USA

- 1 Butylamino-phenoxy-propanol-acetate (BPPA) is a new topical oculoselective β -adrenoceptor blocker for the reduction of intraocular pressure (IOP) in man. Its potency on the airways of normal subjects was identical with that of placebo. A study was carried out to determine the potential of BPPA to cause bronchoconstriction in mild asthmatics ($FEV_1 \geq 60\%$ predicted) with normal IOP.
- 2 Twelve nonsmoking outpatients who bronchoconstricted to 0.25 or 0.50% of timolol eye drops (fall in FEV_1 $23.33 \pm 1.20\%$ (mean $\pm$ s.e. mean), range 16–30) were investigated in this double-masked, randomized, 3-period, crossover study. On three different occasions six incremental concentrations of BPPA (range: 0.1–2%; maximum cumulative concentration 4%), timolol (0.1–1%; 2%), and placebo were administered bilaterally until bronchoconstriction (decrease in $FEV_1 \geq 20\%$ and in specific airway conductance (sGaw) $\geq 35\%$ simultaneously) or the maximum cumulative concentration was reached.
- 3 Airway response was measured as change in FEV_1 and sGaw and dose-response curves to timolol, BPPA and placebo were performed. IOP was measured 3 h after the highest concentration of each study day.
- 4 Timolol caused dose-dependent falls in FEV_1 and sGaw as well as clinical symptoms of respiratory distress in all subjects. The median cumulative concentrations of timolol required to decrease FEV_1 by 20% and sGaw by 35% were 0.98% and 1.53%. Neither placebo ($P > 0.05$) nor BPPA ($P > 0.05$) caused a significant change in sGaw. A fall in FEV_1 by 20% not accompanied by a simultaneous fall in sGaw by 35% was found in four subjects following BPPA and in five subjects following placebo. As none of these subjects showed clinical symptoms of respiratory distress these falls in FEV_1 were not interpreted to result from bronchoconstriction.
- 5 Both active drugs reduced IOP equally effectively ($P < 0.05$), whereas placebo did not change IOP ($P > 0.05$).
- 6 The fact that cumulative concentrations of BPPA up to 4% had no effect on sGaw confirms the hypothesis that ophthalmic BPPA does not cause bronchoconstriction in asthmatics. In respect of its mode of action BPPA would have a greater safety margin than timolol and even betaxolol. Topical oculoselectivity may be an important aspect of drug safety.

Keywords ophthalmic β -adrenoceptor blockers butylamino-phenoxy-propanol-acetate BPPA asthma lung function intraocular pressure

Introduction

Ophthalmic β -adrenoceptor blockers are widely used for the reduction of intraocular pressure (IOP) in patients with glaucoma and ocular hypertension. They may be absorbed into the systemic circulation (Alvan *et al.*, 1980) and can cause unwanted systemic effects such as asthma, decrease in heart rate, congestive heart failure, and syncope (Britman, 1979; Jones & Ekberg, 1979). Especially noncardioselective β -adrenoceptor blockers such as timolol, metipranolol, carteolol, levobunolol, pindolol, befunolol, and others result in systemic β -adrenoceptor blockade in healthy volunteers (Bacon *et al.*, 1989; Berlin *et al.*, 1987; Cervantes *et al.*, 1986; LeJeunne *et al.*, 1990; Mekki *et al.*, 1984) as well as in patients with obstructive airway disease (Cervantes *et al.*, 1986; Dunn *et al.*, 1986; Hugues *et al.*, 1987; Schoene *et al.*, 1984; Spiritus & Casciari, 1985). Systemic β -adrenoceptor blocking effects have been reported to be minimal or completely absent in patients with obstructive airway disease following cardioselective ocular betaxolol (Brooks *et al.*, 1987; Cervantes *et al.*, 1986; Dunn *et al.*, 1986; Ofner & Smith, 1987; Schoene *et al.*, 1984; Spiritus & Casciari, 1985; Van Buskirk *et al.*, 1986).

BPPA, (S)-3-tert-butylamino-1-[4[2(hydroxy)ethyl]-phenoxy] 2-propanol acetate, a new topical oculo-selective β -adrenoceptor antagonist, lowers IOP without producing evidence of systemic β -adrenoceptor blockade (Bauer *et al.*, 1991; Sugrue *et al.*, 1988). BPPA is the prodrug of the alcohol L-652,698, both are non-selective β -adrenoceptor blockers. Hydrolysis by corneal esterases at the ocular receptor sites leads to the active substance L-652,698. The rapid oxidation in the systemic circulation to inactive carboxylic acid metabolites explains the lack of systemic β -adrenoceptor blockade following ocular administration (Sugrue *et al.*, 1988).

Studies in healthy volunteers showed that BPPA was as effective as timolol in reducing IOP but did not antagonize the dose-response of inhaled isoprenaline on airway calibre, heart rate, and finger tremor (Bauer *et al.*, 1991). These findings provide sufficient safety to further evaluate BPPA in asthmatics. The aim of this study was to assess bronchoconstriction following cumulative concentrations (CC) of the ophthalmic β -adrenoceptor blockers BPPA, timolol, and placebo in asthmatics who bronchoconstricted to timolol.

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Methods

Full written informed consent was obtained from all subjects after approval of the local hospital ethics committee.

Subjects

Patients were initially selected if they were aged 21 to 65 years, were non-smokers (never smokers or ex-

smokers > 5 years), had a documented history of asthma and an actual FEV₁ $\geq$ 60% of the predicted value and required only inhaled β -adrenoceptor agonists. Selection of subjects was further based on normal physical and ocular examination, normal routine laboratory profile (blood count, chemistry screen, urine analysis), ECG (standard 12-lead), and chest X-ray. Subjects were excluded if they had evidence or history of ocular symptoms, diseases or trauma, contact lenses, narrow anterior chamber angles, concomitant ocular or regular medication (except inhaled β -adrenoceptor agonists). They were then screened to see whether they bronchoconstricted following the administration of timolol eye drops (decrease in FEV₁ of > 10% but $\leq$ 30%). One drop of 0.25% timolol maleate was instilled into each eye, after which FEV₁ was measured at 30 and 60 min. If the fall in FEV₁ was less than 10% at 60 min, a second dose of 0.25% timolol was given and lung function repeated. Salbutamol (0.4 mg by metered dose inhaler) was given to reverse bronchoconstriction and FEV₁ was measured 30 min after inhalation. Subjects were then observed for an 8 h period and received repeated inhalations of salbutamol when necessary. Sixteen subjects, who showed a fall in FEV₁ of $22.75 \pm 1.02\%$ (mean $\pm$ s.e. mean, range 16–30%) after either dose of timolol, had to be recruited for the main study.

Techniques

FEV₁ (best of three measurements) and specific airway conductance (sGaw; mean of five individual readings) were measured by spirometry and body plethysmography (Transferscreen II and Bodyscreen II, Jaeger, Wuerzburg, Germany). Heart rate, blood pressure (Korotkoff phases I and V) were registered after standing for 1 min. Tonometry by applanation (Goldmann) was used for measurement of IOP.

Protocol design

The study was carried out in a randomized, double-masked, three-period, crossover, and placebo-controlled design on 3 different days (at the same time of day) separated by at least 1 week. All subjects had to abstain from inhaled β -adrenoceptor agonists 12 h prior to each study day. Absence of ocular symptoms was verified on each occasion. After resting 30 min, baseline parameters were recorded.

Dosing regimen

Six increasing concentrations of ophthalmic solutions of BPPA (0.1%, 0.15%, 0.25%, 0.5%, 1.0%, 2.0%; maximum CC 4.0%), and of timolol (0.1%, 0.15%, 0.25%, 0.5%, 1.0%, 0.0%; maximum CC 2.0%), and six repeated doses of placebo (vehicle of BPPA), respectively, were administered by ocumeter (1 drop in each eye by the ophthalmologist) at 20 min intervals. The highest concentration of BPPA was matched by a final placebo dose for the timolol-response.

Procedure

Measurement of the parameters started 15 min after each dosing and lasted 5 min. The order was sGaw, FEV₁, heart rate and blood pressure. Dosing continued until all six CC had been given, or until bronchoconstriction was measurable (decrease in FEV₁ $\geq$ 20% and sGaw $\geq$ 35% simultaneously). Salbutamol was given to reverse bronchoconstriction when necessary. Subjects were observed for a further 8 h period and received repeated inhalations of salbutamol or fenoterol when necessary. Lung function was measured after 2, 4, and 8 h. On each study day IOP was measured 3 h after the highest concentration administered. At the conclusion of the study a physical examination, ECG, laboratory profile, and complete ocular examination were repeated.

Statistics

Data are presented as arithmetic mean $\pm$ s.e. mean. Analysis of variance (ANOVA) for repeated measures was performed on the raw data using the 'SPSS plus' software package (SPSS Inc., Chicago, Ill.). The Student's *t*-test was used when appropriate. Dose-response curves were constructed for each subject by plotting the log concentration of each drug against FEV₁ and sGaw. The cumulative provocative concentration (PC) producing a 20% decrease in FEV₁ (PC₂₀FEV₁) and a 35% decrease in sGaw (PC₃₅sGaw) from baseline was calculated by linear interpolation from the dose-response curves for each of the 12 subjects for each treatment. ANOVA on the ranks was used to compare the PC from each of the treatments. This nonparametric analysis was used because BPPA and placebo caused insufficient change from baseline in most subjects. With BPPA, the respective PC was set equal to 4% in these cases, and with placebo the respective PC was set equal to dose number 7 (greater than the maximum dose number 6). A *P* value of < 0.05 was considered as being of significance.

Results

Four subjects discontinued due to different reasons not related to study treatment. Subject 3 missed the last test day twice after completion of two periods (placebo, BPPA). Subjects 8 and 9 were excluded because of the development of an upper respiratory tract infection during the wash out period following the placebo test day. These subjects showed a decrease in baseline parameters and needed additional treatment (systemic corticosteroids, oral β -adrenoceptor agonists). Subject 12 discontinued after completion of two periods (BPPA, timolol) for personal reasons. Characteristics of the 12 subjects who completed the study are given in Tables 1 and 2.

FEV₁ and sGaw

There was no difference between the baseline values of FEV₁ or sGaw on any of the test days ($P > 0.05$) (Table 3). After challenge with timolol all 12 subjects had a fall in FEV₁ of 20% or more and a fall in sGaw of 35% or more combined with clinical symptoms of respiratory distress (Figures 1 and 2). After timolol a simultaneous decrease in both parameters at the same CC could be found in nine subjects, in the remaining three subjects the decrease in FEV₁ occurred after a lower CC than for sGaw.

After challenge with BPPA and placebo sGaw remained relatively unchanged and a decrease by 35% could not be found in any of the subjects. A fall in FEV₁ of 20% or more could be registered after BPPA in four patients (subject 4, 5, 11, 15) and after placebo in five patients (subject 4, 5, 10, 11, 16). Neither with BPPA nor with placebo could a concomitant decrease in sGaw by 35% be registered in any of these subjects. Except for a tickle in the throat and a consecutive tussive irritation during measurements of FEV₁ clinical symptoms of respiratory distress could not be observed.

Table 1 Demographic data and bronchodilator reversibility test in 12 asthmatics

Subject	Sex/ Smoking	Age (years)	Height (cm)	Weight (kg)	Duration (years)	Baseline			Post-salbutamol* % Change		Month before timolol sensitivity test
						FEV ₁ (l)	FEV ₁ (% pred)	sGaw (s ⁻¹ kPa ⁻¹)	FEV ₁	sGaw	
1	M/NS	38	171	71	4	2.66	71	0.39	+23	+161	2
2	M/NS	65	174	84	2	2.11	68	0.31	+27	+164	3
4	M/ES	48	170	88	6	2.57	75	0.52	+17	+86	4
5	F/ES	48	155	65	9	1.46	63	0.47	+35	+100	3
6	F/NS	55	153	63	4	1.38	67	0.40	+28	+97	3
7	F/NS	39	168	62	3	2.14	70	0.68	+18	+20	2
10	M/NS	41	178	80	4	2.42	61	0.33	+32	+172	4
11	F/NS	26	168	69	3	2.20	65	0.29	+24	+196	3
13	M/ES	46	179	80	5	2.67	69	0.48	+19	+122	3
14	M/NS	41	175	68	4	2.92	76	0.74	+19	+64	1
15	F/NS	39	163	64	3	2.03	71	0.67	+26	+76	1
16	M/NS	30	172	69	3	2.62	65	0.36	+22	+175	2
Mean		43.00	168.83	71.91	4.16	2.26	68.41	0.47	+24.16	+119.41	2.58
s.e. mean		3.02	2.37	2.54	0.53	0.13	1.31	0.04	1.63	15.65	0.28

*Measurements 30 min after inhalation of 0.4 mg applied by metered dose inhaler
NS: Never smoker, ES: ex-smoker (> 5 years).

Table 2 Prestudy selection with ophthalmic timolol in the 12 asthmatics who completed the main study

Subject	Baseline			Post-timolol* Maximum % change		Post-salbutamol* % change	
	FEV ₁ (l)	FEV ₁ (% pred)	sGaw (s ⁻¹ kPa ⁻¹)	FEV ₁	sGaw	FEV ₁	sGaw
1	3.08	82	0.42	-25	-41	-3	+75
2	2.76	89	0.42	-19	-56	+13	+24
4	2.96	86	0.74	-20	-54	+12	+55
5	1.99	86	0.82	-16	-55	+12	+221
6	1.96	95	0.75	-22	-77	+6	+81
7	2.84	93	0.71	-24	-59	+3	+64
10	3.63	91	1.05	-20	-52	-7	-5
11	2.77	82	0.97	-25	-66	+4	-26
13	3.37	87	0.75	-30	-42	-4	+6
14	3.36	87	0.92	-29	-53	-8	+14
15	2.23	78	1.03	-27	-55	+20	+41
16	3.14	78	1.00	-23	-55	+11	-17
Mean	2.84	86.16	0.79	-23.33	-55.41	+4.91	+44.41
s.e. mean	0.15	1.57	0.06	1.20	2.75	2.59	19.08

*Measurements 30 and 60 min after instillation of 0.25% administered bilaterally. If no bronchoconstriction occurred, a second dose of 0.25% was given and the procedure repeated.

+Measurements 30 min after inhalation of 0.4 mg applied by metered dose inhaler.

Table 3 Baseline values before administration of ophthalmic β -adrenoceptor blockers*

	Placebo	BPPA	Timolol
FEV ₁ (l)	2.87 $\pm$ 0.19	2.89 $\pm$ 0.18	2.79 $\pm$ 0.18
sGaw (s ⁻¹ kPa ⁻¹)	1.00 $\pm$ 0.08	1.00 $\pm$ 0.08	0.85 $\pm$ 0.04

* Values are shown as mean $\pm$ s.e. mean. There were no significant differences between any of the measured variables (ANOVA).

With the exception of subject 4 on BPPA and subject 16 on placebo higher FEV₁ values were found at the following CC (Figures 1 and 2).

Following timolol, salbutamol caused a mean increase in FEV₁ from 1.79 to 2.84 l, i.e. from 64% to 102% of baseline FEV₁ (Table 4). The individual FEV₁ values after challenge with BPPA and placebo are presented

Table 4 Mean FEV₁ values before and after timolol challenge and after salbutamol inhalation in 12 subjects

	Baseline	Post-timolol	Post-salbutamol* (0.4-1.2 mg)
Mean	2.79	1.79	2.84
s.e. mean	0.16	0.14	0.20
% of baseline	100	64	102

*Measurement 30 min after inhalation of salbutamol by metered dose inhaler.

for those subjects who showed a fall in FEV₁ by 20% or more without concomitant decrease in sGaw by 35% (Table 5). In all these subjects sGaw did not change and FEV₁ returned to baseline without inhalation of a β -adrenoceptor agonist during the observation period.

Table 5 Individual FEV₁ baseline values (l) and changes (% of baseline) following BPPA and placebo of those subjects who showed a fall in FEV₁ by 20% or more without a concomitant fall in sGaw by 35% and without concomitant symptoms of respiratory distress. In none of the subjects was a β -adrenoceptor agonist given after the challenge or during the observation period

Subject	Treatment	FEV ₁ (% of baseline)					
		Baseline (l)	After eye drops		Observation period (h)		
			Maximum fall	After CC 6*	2	4	8
4	Placebo	2.97	70	94	102	97	95
	BPPA	3.03	61	61	97	95	99
5	Placebo	2.05	62	86	97	104	101
	BPPA	2.09	77	87	103	98	105
10	Placebo	3.51	57	85	95	96	92
11	Placebo	2.73	66	82	94	102	96
	BPPA	2.89	76	90	97	106	104
15	BPPA	2.43	76	82	100	93	96
16	Placebo	3.71	41	48	96	104	97

*CC 6 = the highest cumulative concentration of BPPA (4%) or the sixth dose of placebo.

Figure 1 Individual concentration-response curves (subject 1, 2, 4, 5, 6, 7) for timolol (■), BPPA (▲), and placebo (●), against percentage of baseline FEV₁ (left) and sGaw (right).

None of the 12 subjects reported clinical symptoms of respiratory distress and a decrease in PEFR during the subsequent night.

PC₂₀FEV₁, PC₃₅sGaw

The individual values of PC₂₀FEV₁ and PC₃₅sGaw are presented in Table 6. With BPPA the median of PC₂₀FEV₁ was greater than 4% (the largest CC; range 1.33 to > 4%) compared with 0.98% (range 0.23 to 2%) after timolol. With BPPA, the median of PC₃₅sGaw was greater than 4% compared with 1.53% (range 0.68 to 2%) after timolol. Statistics on PC₂₀FEV₁ and PC₃₅sGaw showed no significant differences between BPPA and placebo ($P > 0.05$), whereas the differences between timolol and both placebo and BPPA proved to be significant ($P < 0.01$).

Figure 2 Individual concentration-response curves (subject 10, 11, 13, 14, 15, 16) for timolol (■), BPPA (▲), and placebo (●), against percentage of baseline FEV₁ (left) and sGaw (right).

Ocular examination

Burning and tearing occurred more frequently with BPPA than with timolol and placebo. Foreign body sensation occurred with all solutions. The symptoms were mild, occurred immediately postdose, and usually lasted 3 min or less. IOP (mmHg) was significantly lower with both BPPA (10.9 ± 0.4 dext.; 11.0 ± 0.3 sin; $n = 10$ for technical reason) ($P = 0.0001$; $P = 0.0001$) and timolol (9.6 ± 0.3 ; 10.0 ± 0.4) ($P = 0.0001$; $P = 0.0001$) compared with placebo (13.3 ± 0.5 ; 13.6 ± 0.6). There was no significant difference between BPPA and timolol ($P = 0.111$; $P = 0.210$). No other changes could be obtained following the active substances.

Table 6 Effect of the ophthalmic β -adrenoceptor blockers on PC₂₀FEV₁ and PC₃₅sGaw

Subject	Placebo		BPPA		Timolol	
	PC ₂₀ FEV ₁ (dose)	PC ₃₅ sGaw (dose)	PC ₂₀ FEV ₁ (%)	PC ₃₅ sGaw (%)	PC ₂₀ FEV ₁ (%)	PC ₃₅ sGaw (%)
1	7	7	> 4.00	> 4.00	1.83	1.57
2	7	7	> 4.00	> 4.00	0.55	0.68
4	5*	7	2.93*	> 4.00	0.70	0.75
5	5*	7	1.89*	> 4.00	1.20	1.82
6	7	7	> 4.00	> 4.00	0.60	0.69
7	7	7	> 4.00	> 4.00	0.75	0.93
10	5*	7	> 4.00	> 4.00	0.23 ⁺	1.50
11	5*	7	1.85*	> 4.00	0.87 ⁺	1.59
13	7	7	> 4.00	> 4.00	1.72 ⁺	2.00
14	7	7	> 4.00	> 4.00	1.10	1.70
15	7	7	1.33*	> 4.00	1.26	1.45
16	5*	7	> 4.00	> 4.00	2.00	2.00

*Fall in FEV₁ by $\geq 20\%$ not accompanied by a fall in sGaw by $\geq 35\%$.

⁺Fall in FEV₁ by $\geq 20\%$ not accompanied by a simultaneous fall in sGaw by $\geq 35\%$ at the same cumulative concentration.

Heart rate, blood pressure

There were no significant changes in heart rate ($P = 0.522$) and systolic ($P = 0.998$) or diastolic ($P = 0.829$) blood pressure.

Drug safety

No other clinical, laboratory or ECG adverse experiences were obtained.

Discussion

Our results show a good coincidence with those of other authors concerning bronchoconstriction following ophthalmic timolol in selected asthmatics (Cervantes *et al.*, 1986; Dunn *et al.*, 1986; Richards & Tattersfield, 1987; Schoene *et al.*, 1984; Spiritus & Casciari, 1985). The hypothesis derived from previous studies in normal subjects that BPPA does not cause bronchoconstriction in asthmatics was confirmed by our data on sGaw, and with limitation, our data on FEV₁ (Bauer *et al.*, 1991; Maclure *et al.*, 1987). The quantitative assessment of the bronchial β -adrenoceptor blockade as well as the β -adrenoceptor blocking effects on heart rate and muscle tremor can be assessed more accurately by measuring the displacement of the β -agonist dose-response curves in normal subjects (Bauer *et al.*, 1991; Tattersfield & Keeping, 1979).

In our study the subjects with a fall in FEV₁ following BPPA and/or placebo, received all doses of the challenge regime because they had definitely unchanged traces of sGaw. These subjects did not show any clinical symptoms of respiratory distress such as chest tightness, wheezing, shortness of breath, dyspnoea, and cough as occurred in all subjects with timolol. Moreover, on the placebo and BPPA test days these subjects did not need a β_2 -adrenoceptor agonist during the respective observation period. At the points of measurement with an isolated fall in FEV₁ subjects only complained of a tickle in the throat and consecutive tussive irritation during the

forced manoeuvres. None of these subjects was irritated or felt uncomfortable during the sGaw measurements. We also can exclude that in those subjects, who showed no fall in FEV₁ and sGaw following BPPA, improper and insufficient administration of the eye drops was the reason for a missing reaction to the noncardioselective BPPA. Blinking or overflow did not occur in any of the subjects. Therefore, the fall in FEV₁ following placebo, which definitely does not influence airway calibre, and following BPPA can hardly be caused by bronchoconstriction and must be interpreted false positive.

Flow measurements such as FEV₁ have a good reproducibility and adequate sensitivity (Tattersfield & Keeping, 1979). But in studies with repeated lung function measurements within short intervals, evaluation of sGaw may offer the advantage to avoid full inspiration and forced expiratory manoeuvres, which can provide increased sensitivity (Tattersfield & Keeping, 1979). The very low flow and quasi-static conditions of sGaw measurements (Tattersfield & Keeping, 1979) were obviously tolerated better by the subjects investigated. In our study PC₂₀FEV₁ and PC₃₅sGaw were not always reached simultaneously after the same concentration of the respective ophthalmic solution. In all these observations PC₂₀FEV₁ was reached at a lower CC than PC₃₅sGaw. Considering the conflicting results on FEV₁ and sGaw body plethysmography may have prevented a premature termination of the dosing of the respective ophthalmic solution. Especially with BPPA, evaluation of PC₂₀FEV₁ alone would have led to wrong conclusions, at least in some subjects.

An ideal ophthalmic β -adrenoceptor blocker should effectively reduce IOP without producing systemic β -adrenoceptor blockade. Previously, attempts have been made to obtain a high intraocular concentration of drugs after topical instillation. It has been shown that a more lipophilic prodrug can enhance ocular penetration e.g. the dipivalyl ester of adrenaline (Kaback *et al.*, 1976), and the *o*-pivalyl ester of a carbonic anhydrase inhibitor (Sugrue *et al.*, 1985). In asthmatic subjects the (R)-enantiomer of timolol caused falls in sGaw and FEV₁ being approximately four times less potent than timolol (Richards & Tattersfield, 1987). Since the difference in

potency is similar to that in IOP the (R)-enantiomer of timolol would not have a greater safety margin than timolol (Richards & Tattersfield, 1987). Recently it has been suggested that betaxolol should be preferred to any other ophthalmic β -adrenoceptor blocker in case of positive contraindications (LeJeunne *et al.*, 1990). The reason may be its cardioselectivity, lipophilicity and greater degree of plasma protein binding compared with timolol (Buckley *et al.*, 1990). Experimental studies with cardioselective ocular β -adrenoceptor blockers in healthy volunteers (Cervantes *et al.*, 1986; LeJeunne *et al.*, 1990) as well as clinical studies in asthmatics (Brooks *et al.*, 1987; Cervantes *et al.*, 1986; Dunn *et al.*, 1986; Ofner & Smith, 1987; Schoene *et al.*, 1984; Spiritus & Casciari, 1985; Van Buskirk *et al.*, 1986) demonstrated a lack of measurable changes in airway calibre. On the other hand, systemic adverse effects have been occasionally reported with betaxolol (Bauer *et al.*, 1991; Harris *et al.*, 1986; LeJeunne *et al.*, 1990; Nelson & Kuitsky, 1987; Weinreb *et al.*, 1988; Zabel & MacDonald, 1987). Different methods applied to investigate ophthalmic β -adrenoceptor blockers may explain the controversial findings. As drainage through the lacrimal duct and absorption from the nasal mucosa makes it almost

impossible to avoid systemic effects from ophthalmic β -adrenoceptor blockers, and since there is no hepatic first-pass effect, significant high concentrations can reach systemic target organs (Akers *et al.*, 1977; Shell, 1982). Thus a cardioselective β -adrenoceptor blocker may reduce, but not abolish, systemic side effects.

The demand to achieve precise and direct effects at the site of action without systemic side effects has obviously not been reached so far (Stella *et al.*, 1985). BPPA appears to solve this problem because, as a prodrug, it is inert until hydrolyzed at its ocular site of action. The active drug is then rapidly oxidized to inactive metabolites in the systemic circulation. Ophthalmic BPPA was as effective as timolol in reducing IOP. In respect of its mode of action BPPA would have a much greater safety margin than timolol and even betaxolol. Topical oculoselectivity resulting in complete absence of systemic β -adrenoceptor blockade may be an important aspect of drug safety.

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