Br. J. clin. Pharmac. (1985), **20**, 459–462

Bronchial β-adrenoceptor blockade following eyedrops of timolol and its isomer L-714,465 in normal subjects

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1 The R-entantiomer of timolol, L-714,465, is considerably less potent as a β_1- and β_2-adrenoceptor antagonist in animals than timolol, whilst only slightly less potent in reducing intraocular pressure. If the same was true in man L-714,465 would have potential benefits over timolol in the treatment of glaucoma.
2 The extent of bronchial β-adrenoceptor blockade following one eyedrop in each eye of timolol 1% and L-714,465 1% was compared in six normal subjects, by measuring the displacement of the bronchodilator dose-response curve to isoprenaline following each drug compared to the isoprenaline dose-response curve after placebo eyedrops (methylcellulose).
3 There was no significant difference between the dose-response curves to L-714,465 and placebo, but a significant displacement of the dose-response curve following timolol. The geometric mean dose ratio following timolol (21) differed significantly from that following L-714,465 (1.6).
4 Heart rate at the end of the isoprenaline dose-response study was lower after timolol, despite the fact that subjects had received higher doses of isoprenaline. The trend was in the same direction after L-714,465 when compared with placebo though less marked.
5 L-714,465 clearly causes less β-adrenoceptor blockade than timolol when given as 1% eyedrops. The effects of L-714,465 1% on the airways and heart rate did not differ significantly from placebo in these six subjects but the pattern of response would be most consistent with L-714,465 having some β-adrenoceptor blocking activity though considerably less than timolol.

Keywords timolol L-714,465 β-adrenoceptor blockade

Introduction

Timolol eyedrops are widely used for the treatment of glaucoma. Although contraindicated in patients with asthma (Jones & Ekberg, 1980; Schoene *et al.*, 1981, 1984; Lawrssen & Bjerrum, 1982) the risk is often not appreciated and in the United States 200 possible major timolol-induced respiratory events have been reported to the National Registry of drug induced ocular side effects in Oregon, including 16 deaths (Fraunfelder & Barker, 1984). The R-entantiomer of timolol (L-714,465) appears to be considerably less potent as a β-adrenoceptor antagonist in animals than timolol whilst only slightly less potent in reducing intraocular pressure (unpublished data). If this were true in man L-714,465 might be a safer drug to use for the

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treatment of glaucoma. This study set out to measure bronchial β-adrenoceptor blockade in normal subjects following eyedrops of timolol (1%) and L-714,465 (1%) on separate days. Bronchial β-adrenoceptor blockade was measured as the displacement of the inhaled isoprenaline bronchodilator dose-response curve relative to that following placebo (Tattersfield *et al.*, 1984).

Methods

Seven normal non-smoking subjects aged 24–31 years with no history of asthma or eye disease were recruited for the study. Specific airway conductance (sGaw) was measured in the body plethysmograph on line to a microprocessor (Apple 2) which calculated mean values of airway resistance (Raw) and sGaw over 10 s and thoracic gas volume (TGV) over 4 s (Shah *et al.*, 1980). Subjects gave informed consent for the study, which was approved by the Southampton Ethics Committee.

Subjects attended on 3 days at least 1 week apart. After resting for a few minutes, five baseline measurements of sGaw were made. Subjects then received one eyedrop in each eye of either methylcellulose, timolol 1% or L-714,465 1% in a double-blind manner according to a balanced design. When subjects returned 1.5 h later 10 ml venous blood was taken for subsequent drug assay. Three further measurements of sGaw were carried out and followed by an isoprenaline dose-response study. The subject inhaled increasing doses of isoprenaline at 5 min intervals from specially prepared metered dose inhalers to achieve cumulative doses of isoprenaline of 10, 20, 100, 340, 740, 1940, 3940 and 7000 μg. Studies were discontinued when heart rate exceeded 100 beats min^{-1}.

Analysis of results

Mean baseline values of sGaw and TGV before and after each drug were compared by Wilcoxon's paired rank test. Dose-response curves were accepted if there were three points on the steep part of the curve. A regression of Δ sGaw on log dose isoprenaline was calculated by the method of least mean squares and subjected to an analysis of covariance for position and slope. The maximum response to isoprenaline was taken as the mean of the two highest values in any of the three studies. The dose of isoprenaline causing 50% of this response was read directly from the dose-response curves. Student's *t*-test was used to compare geometric mean dose ratios and mean heart rate values at the end of the study.

Results

One subject noted a fall in visual acuity from 6/5 to 6/12 on the Snellen chart following both timolol 1% and L-714,465 1%. This returned to normal over 1–2 h. The higher doses of inhaled isoprenaline caused palpitations in all subjects on at least one occasion.

Six of the seven subjects had good dose-response curves following isoprenaline. Subject 7 however had a 12% fall in sGaw following timolol, only a 23% increase in sGaw following placebo, and failed to have three points on the steep part of the dose-response curve following timolol so that a valid maximum dose of isoprenaline value could not be obtained. His results have therefore been excluded from further analysis. There was no change in mean baseline sGaw following any of the eyedrops (Table 1). The analysis of covariance showed no difference in the slope of the isoprenaline dose-response curve after any of the eyedrops. There was no difference between the position of the dose-response curves for L-714,465 and placebo; the curves following timolol were significantly displaced ($P < 0.001$). Isoprenaline dose ratios ranged from 0.3 to 5 following L-714,465 1% with a geometric mean dose ratio of 1.6, and from 3.9 to 61 following timolol 1% with a geometric mean dose ratio of 21 (Table 2). Serum concentrations of timolol and L-714,465 are shown in Table 3.

Studies were frequently stopped before 7000 μg isoprenaline had been given because of palpitations or because heart rate exceeded 100 beats min^{-1}. The dose of isoprenaline at which this occurred following the three drugs and the mean heart rate at this time has been tabulated as an index of cardiac β-adrenoceptor blockade (Table 4). Mean heart rate after timolol was significantly lower than heart rate after placebo ($P < 0.05$) despite the fact that subjects had inhaled higher doses of isoprenaline. Heart rate after placebo and L-714,465 did not differ significantly.

Discussion

Timolol, a non-selective β-adrenoceptor antagonist, is absorbed from ocular, nasal and gastric mucosa. There was a twofold variation in timolol serum concentrations between subjects and a threefold variation for L-714,465 with a mean serum level of between 1 and 2 ng g^{-1} for both

Table 1 Mean baseline values of specific airway conductance (sGaw) and thoracic gas volume (VTG) before and 90 min after placebo, L-714,465 and timolol

		Placebo		*L-714,465*		*Timolol*	
		Before	*After*	*Before*	*After*	*Before*	*After*
sGaw	mean	1.48	1.48	1.41	1.3	1.3	1.26
($s^{-1}kPa^{-1}$)	s.e. mean	±0.18	±0.16	±0.18	±0.16	±0.16	±0.15
VTG	mean	4.27	4.28	4.34	4.26	4.25	4.41
(l)	s.e. mean	±0.46	±0.44	±0.48	±0.46	±0.42	±0.44

None of the changes was significant

drugs. This compares with peak mean values of around 40 ng ml^{-1} after 10 mg oral timolol in healthy volunteers (Else *et al.*, 1978; Davies 1979), and 100 ng ml^{-1} after the higher dose of 0.4 mg kg^{-1} (Wilson *et al.*, 1982). A reduction in exercise heart rate has been demonstrated in normal subjects after the lower dose of 0.5% timolol eyedrops (Mekki *et al.*, 1984). The heart rate at the end of each dose-response study showed considerable intersubject variation, but was lower in the subjects after timolol than after L-714,465 or placebo despite having inhaled higher doses of isoprenaline. Heart rate tended to be lower following L-714,465 compared with placebo, but the difference was less marked and not significant.

Table 2 Isoprenaline dose causing a 50% maximum response in sGaw and dose ratios

	*Isoprenaline dose causing 50% response**			*Dose-ratios*	
Subject	*Placebo*	*L-714,465*	*Timolol*	*L-714,465*	*Timolol*
1	32	85	125	1.6	3.9
2	37	75	880	2.02	23
3	90	100	3600	1.1	40
4	42	210	2600	5	61
5	26	54	480	2	18
6	150	50	3800	0.3	25
				—	—
			geometric mean	1.5	21
			+1 s.e.	2.1	30.5
			−1 s.e.	1.05	15

* Dose-response curves started 90 min after administration of the eyedrops.

Table 3 Serum concentrations of timolol and L-714,465*

Subject	*Placebo*	*L-714,465 1% (ng g^{-1} serum)*	*Timolol 1% (ng g^{-1} serum)*
1	0	0.5	1.2
2	0	1.4	1.3
3	0	1.1	2.4
4	0	1.6	1.4
5	0.2	1.2	1.2
6	0	0.8	1.7
	—	—	—
		1.10	1.53 mean
		0.37	0.42 SD

0 = below detection limit (< 0.2 ng g^{-1} serum).
* blood taken 90 min after administration of eyedrops.

Bronchoconstriction is well documented following the administration of timolol eyedrops to asthmatic subjects (Jones & Ekberg, 1980; Schoene *et al.*, 1981, 1984; Lawrssen & Bjerrum, 1982) and was attributed to bronchial β-adrenoceptor blockade. It was anticipated therefore that some bronchial β-adrenoceptor blockade would be demonstrable in normal subjects despite serum levels of timolol which are approximately one twentieth of those seen after oral administration. This study confirmed our expectation since 1 drop of timolol 1% eyedrops in each eye caused appreciable bronchial β-adrenoceptor blockade in six normal subjects. The dose ratio of 21 following timolol eyedrops is very similar to that seen in previous studies with 40 mg oral propranolol (Gribbin *et al.*, 1979).

Table 4 Number of subjects completing study after each dose of isoprenaline, and mean heart rate (HR) on completion

Dose of isoprenaline (μg)	Placebo		L-714,465		Timolol	
	Number completing	Mean HR (beats min^{-1})	Number completing	Mean HR (beats min^{-1})	Number completing	Mean HR (beats min^{-1})
740	2	95				
1940	1	120	2	100		
3940	2	124	3	98	1	80
7000	1	120	1	108	5	84

We would anticipate therefore that oral timolol 10 mg would cause appreciably more bronchial β-adrenoceptor blockade than propranolol 40 mg.

The changes following L-714,465 were small and statistically indistinguishable from placebo. The difference in dose ratios for L-714,465 and timolol is unlikely to be due to differences in absorption since serum levels of L-714,465 were 70% of those seen with timolol on average. The results confirm that L-714,465 has less β_2-adrenoceptor blocking activity than timolol. The study design does not allow us to say whether L-714,465 has some β_2-adrenoceptor blocking activity albeit less than timolol, or none. The mean dose ratio for L-714,465 is similar to that seen with oral atenolol 100 mg or metoprolol 200 mg in different subjects in previous studies (Gribbin *et al.*, 1981; Tattersfield *et al.*, 1984). The fact that following L-714,465 all but one subject had a dose ratio above 1, and that mean heart rate at completion of the study was lower than after placebo strongly suggest that L-714,465 has some β-adrenoceptor blocking activity.

We gratefully acknowledge financial support from Merck Sharp & Dohme who also supplied the eye-drops, and we thank Dr Mike Campbell, Community Medicine Department, Southampton General Hospital, for statistical advice and Dr K. Widmark, University of Stockholm, for serum assays of timolol and L-714,465.

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(Received 12 March 1985, accepted 18 July 1985)