The effects of time and dose on the relative β_1 - and β_2 -adrenoceptor antagonism of betaxolol and atenolol

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- 1 Six normal subjects were given single oral doses of betaxolol 10 mg (B10), 40 mg (B40), 80 mg (B80); atenolol 50 mg (A50), 200 mg (A200); or placebo (PL). Measurements of β_1 -adrenoceptor blockade (reduction of exercise heart rate) and of β_2 -adrenoceptor blockade (attenuation of isoprenaline responses) were made at baseline, and at 2, 4, 6, 8 and 24 h after drug ingestion.
- 2 Mean values for $C_{\max}$ and $t_{\max}$ were as follows: B10 (33 ng ml⁻¹, 3.7 h), B40 (84 ng ml⁻¹, 4.0 h), B80 (179 ng ml⁻¹, 3.7 h); A50 (261 ng ml⁻¹, 2.7 h), A200 (1369 ng ml⁻¹, 2.0 h).
- 3 Reduction of exercise heart rate (EHR) occurred in dose-dependent fashion up to a ceiling at B40 (as % reduction c.f. placebo, at peak and 24 h): B10 16.2 to 10.2%, B40 27.1 to 16.2%, B80 27.0 to 18.7%; A50 20.9 to 9.1%, A200 28.8 to 15.8%. There were also dose-related increases in β_2 -adrenoceptor antagonism (IT₁₀₀ dose ratios, at peak and 24 h): B10 2.1 to 1.2, B40 4.7 to 2.6, B80 6.0 to 4.7; A50 2.0 to 1.2, A200 4.7 to 1.8. There were similar trends for attenuation of heart rate and DBP responses to isoprenaline.
- 4 Ratios of β_1 : β_2 -adrenoceptor antagonism were calculated (as % reduction EHR ÷ IT₁₀₀ dose ratio); to provide an index of β_1 -adrenoceptor selectivity at peak and 24 h: B10 7.7 to 8.5, B40 5.8 to 6.2, B80 4.5 to 4.0; A50 10.5 to 7.6, A200 6.1 to 8.8.
- 5 Thus, increasing doses of betaxolol and atenolol were associated with a progressive decline in the degree of selective β_1 -adrenoceptor blockade. The selectivity ratio was unchanged with betaxolol after 24 h compared with peak effects. In contrast, ratios for A200 and A50 were comparatively reversed after 24 h. This was due to the relatively greater decline in β_2 - and β_1 -adrenoceptor antagonism with A200 and A50 respectively. These findings infer that the use of twice daily low dose atenolol or betaxolol might be of greater benefit in producing effective 24 h β_1 -adrenoceptor blockade, without causing significant antagonism of β_2 -adrenoceptors which occurs with once daily high dose therapy.

Keywords betaxolol atenolol cardioselectivity

Introduction

Betaxolol is one of a group of so called cardioselective β -adrenoceptor blocking drugs (including atenolol, metoprolol and bisoprolol) used in the treatment of angina pectoris and hypertension, which exhibit selective antagonism of cardiac β_1 -adrenoceptors. The term cardioselectivity is a historical misnomer as it is now known that up to 40% of human cardiac β -adrenoceptors are of the β_2 -adrenoceptor subtype (Bristow & Ginburg, 1986; Brodde *et al.*, 1983; Heitz *et al.*, 1983). Lertora and co-workers (1975) originally proposed that selective

β_1 -adrenoceptor blockade may be a relative rather than absolute property. Recent studies with atenolol (Lipworth *et al.*, 1989a,b) have shown that β_2 -adrenoceptor antagonism is a dose-related phenomenon. We have previously shown that conventional doses of betaxolol (10–40 mg) are associated with a partial loss of selective β_1 -adrenoceptor antagonism, although β_2 -adrenoceptor blockade was significantly less than that of propranolol (Irvine *et al.*, 1990). Betaxolol and atenolol both have long half-lives and are currently

recommended in a once daily dosage. The purpose of the present study was to evaluate for the first time the effects of time and dose on the relative antagonism of betaxolol and atenolol on β_1 - (assessed by reduction of exercise heart rate) and β_2 -adrenoceptors (assessed by attenuation of isoprenaline responses).

Methods

Subjects

Written informed consent was obtained from all subjects after approval of the local hospital ethics committee. Six normal subjects (three females) were recruited into the study from a pool of healthy volunteers: mean $\pm$ s.e. mean age 23 ± 2 years (range 19–27 years). All subjects were required to have a normal screen including 12 lead electrocardiogram (ECG), blood biochemistry, and cardiorespiratory examination. Subjects were excluded who had a history of asthma or cardiac arrhythmias.

Protocol

All subjects attended the laboratory at the same time in the morning (08.30 h) on each of the 6 study days. Caffeine consumption was prohibited for 24 h prior to each study day. Treatments were given at weekly intervals in a single-blind double-dummy randomised (by Latin square) cross-over design, and were as follows: placebo (PL); betaxolol 10 mg (B10), 40 mg (B40), 80 mg (B80); atenolol 50 mg (A50), 200 mg (A200). The treatments were given single-blind so as to tailor subsequent isoprenaline infusion rates in constructing dose-response curves. On arrival at the laboratory subjects were placed supine in a temperature controlled room (24 – 26°C), and a cannula was inserted into an antecubital vein which was kept patent with bolus injections of heparinised saline. This was used for administering infusions of isoprenaline as well as for venous sampling to measure plasma drug concentrations. Measurements (finger tremor, heart rate and blood pressure) were made every 5 min during a 20 min resting period in order to establish a true baseline with which to compare successive responses to isoprenaline. Dose-response curves (DRC) were then constructed prior to drug administration using graded infusions of isoprenaline given by an i.v. infusion pump (Braun Perfusor Secura, Braun Medical, Aylesbury, UK).

Isoprenaline solutions were freshly prepared on each study day using ascorbic acid as a preservative. Serial incremental infusions of isoprenaline were given in a dose range of 0.5 – $20 \mu\text{g min}^{-1}$ and each infusion was of 8 min duration. During each infusion heart rhythm was monitored continuously on an ECG oscilloscope with heart rate and blood pressure being recorded every 2 min. Finger tremor was measured each minute between the fifth and eighth minute of the infusion. The means of these values for tremor, heart rate and blood pressure were used for the purposes of analysis. The isoprenaline infusion rate was progressively increased provided that the heart rate had not increased by more than 50 beats

min^{-1} or until adverse effects occurred (palpitations, tremor, dizziness or headache). Approximately four or five different infusion rates were employed such that at least three points were obtained on the steep part of the DRC. Following completion of the infusion, subjects were rested for up to 20 min to allow the heart rate to return to preinfusion baseline values. Subjects then underwent a standardised exercise test (Carruthers *et al.*, 1976) by stepping on and off a box 46 cm high for 3 min at a rate of 32 steps min^{-1} , and heart rate was measured within 5 s of completing the test. Venous blood samples were withdrawn for measurement of plasma drug concentration before each infusion and before each exercise test, and the mean of these values was used for the purpose of analysis.

Following the baseline DRC and exercise test, subjects ingested the tablets with 50 ml water. An identical protocol (resting period, isoprenaline DRC, resting period, exercise test) was repeated at the following times after drug ingestion: 2, 4, 6, 8 and 24 h.

Measurements

Heart rate was monitored continuously and measured the mean of four consecutive R-R intervals from the ECG (Hewlett Packard, Palo Alto, California, USA). Blood pressure was measured with a semi-automated sphygmomanometer (Dinamap Vital Signs Monitor, Critikon, Tampa, Florida, USA). Postural finger tremor was measured by a previously validated method (Lipworth & McDevitt, 1989) using a piezo-resistive accelerometer transducer (Kulite, Ridgefield, New Jersey, USA) taped to the distal phalanx of the middle finger. The results were stored on computer disc and tremor power ($> 2 \text{ Hz}$) was calculated by computer assisted spectral analysis using autocovariance. Plasma betaxolol was measured by gas liquid chromatography using the method described by Bianchetti *et al.* (1979). Plasma atenolol was measured as previously described using high performance liquid chromatography (Lipworth *et al.*, 1989b). The coefficients of variation for analytical imprecision were 3.4% for atenolol and 8.8% for betaxolol.

Statistical analysis

The data were analysed using a 'Statgraphics' software package (STSC Software Publishing Group, USA). For each treatment and variable, individual regression lines were constructed from the steep part of the DRC, using the least squares method. From the individual regression lines, indices were calculated to quantify the doses of isoprenaline required to increase finger tremor by 100% (IT_{100}), heart rate by 25 beats min^{-1} (IH_{25}), and to reduce diastolic blood pressure by 20 mm Hg (ID_{20}), after each treatment. Dose-ratios were calculated by comparison of these indices after β -adrenoceptor blockade with corresponding placebo values. Comparisons between treatments at each time point were made by two-way analysis of variance (ANOVA). A probability level of $P < 0.05$ (two-tailed) was considered as showing a significant difference. Values are shown in the text as mean $\pm$ s.e. mean.

Figure 1 Plasma concentration profiles over a 24 h period of treatment with single oral doses of atenolol 50 mg, 200 mg (a) and betaxolol 10 mg, 40 mg, 80 mg (b). Values are shown as mean and s.e. mean ($n = 6$).

Results

Pharmacokinetics

The pharmacokinetic profiles of betaxolol and atenolol over the 24 h study period are shown in Figure 1. There were appropriate dose-related increases in plasma concentrations of betaxolol and atenolol. Mean values for C_{max} (ng ml⁻¹) and t_{max} (h) were as follows: B10 (33, 3.7), B40 (84, 4.0), B80 (179, 3.7); A50 (261, 2.7), A200 (1369, 2.0). Corresponding values for AUC (ng ml⁻¹ h) were: B10 (233), B40 (1160), B80 (2114); A50 (2127), A200 (10988).

Exercise heart rate

The effects of β -adrenoceptor blockade on exercise heart rate (β_1 -adrenoceptor blockade) are shown in Figure 2. Peak reductions in exercise heart rate were obtained by 2 h for all treatments, and were as follows (as % reduction compared with placebo): B10 $16.2 \pm 1.4\%$, B40 $27.1 \pm 2.0\%$, B80 $27.0 \pm 3.2\%$; A50 $20.9 \pm 1.5\%$, A200 $28.8 \pm 1.5\%$. There were no differences between A50 and B10, although both produced significantly less attenuation compared with A200 and B40. There was a ceiling in the effect of betaxolol on exercise heart rate above the 40 mg dose. There were only small falls in effect on exercise heart rate by 8 h after drug

Figure 2 a) Dose-ratios (compared with placebo) for attenuation of isoprenaline-induced finger tremor response (IT_{100}) at 2, 4, 8 and 24 h after treatment with betaxolol 10 mg (B10), 40 mg (B40), 80 mg (B80); and atenolol 50 mg (A50), 200 mg (A200). Values are shown as mean and s.e. mean ($n = 6$). b) % reduction in exercise heart rate (compared with placebo) after treatment with betaxolol and atenolol.

Table 1 Peak to trough % decline in β_1 - and β_2 -adrenoceptor blockade

	B10	B40	B80	A50	A200
β_1	38	41	30	57	45
β_2	43	45	22	40	62

Values were calculated as $[(\Delta \text{ peak-trough}) \div \text{peak}] \times 100\%$, for β_1 - (% reduction exercise heart rate) and β_2 - (IT_{100} dose-ratios) adrenoceptor antagonism.

ingestion. After a period of 24 h all treatments showed a significant decline in comparison with peak effect, although this was most marked with A50 (Table 1). However, even the lowest doses of betaxolol and atenolol still produced small but significant reductions compared with placebo after 24 h: B10 $10.2 \pm 1.1\%$, B40 $16.2 \pm 4.7\%$, B80 $18.7 \pm 2.6\%$; A50 $9.1 \pm 2.3\%$, A200 $15.8 \pm 2.4\%$.

Isoprenaline responses

Dose-ratios for reduction of isoprenaline-induced finger tremor (β_2 -adrenoceptor blockade) are shown in Figure 2. There were significant dose-related reductions in finger tremor response to isoprenaline for both betaxolol and atenolol. Maximum attenuation occurred within 2–4 h of drug administration. Peak values for IT_{100} dose-ratios were: B10 2.1 ± 0.2 , B40 4.7 ± 1.2 , B80 6.0 ± 1.3 ; A50 2.0 ± 0.2 , A200 4.7 ± 0.8 . The effects of B10 and A50 on finger tremor were significantly less (at 4 h) than B40, B80 and A200. After 24 h the effects of both B10 (1.2 ± 0.1) and A50 (1.2 ± 0.1) had almost completely abated. Higher doses showed a significant persistent degree of attenuation, although the effect of A200 (1.8 ± 0.4) had declined to a greater extent than either B40 (2.6 ± 0.3) or B80 (4.7 ± 1.5) (Table 1).

There were similar trends for betaxolol and atenolol in terms of dose-dependent attenuation of heart rate and diastolic blood pressure responses to isoprenaline

Figure 3 Isoprenaline dose-ratios (compared with placebo) for heart rate (IH₂₅: a), and diastolic blood pressure (ID₂₀: b) at 2, 4, 8 and 24 h after treatment with betaxolol 10 mg (B10), 40 mg (B40), 80 mg (B80); and atenolol 50 mg (A50), 200 mg (A200). Values are shown as mean and s.e. mean ($n = 6$).

(Figure 3). Peak effects occurred within 2–4 h and were significantly greater for B80 and A200 in comparison with B10 and A50. After 24 h the higher doses continued to produce significant effects which were greater for B80 in comparison with A200. Values for IH₂₅ dose-ratios (at peak and 24 h) were as follows: B10 2.3 ± 0.2 to 1.7 ± 0.2 , B40 4.9 ± 1.0 to 3.1 ± 0.3 , B80 6.9 ± 0.7 to 4.2 ± 0.9 ; A50 2.8 ± 0.2 to 1.6 ± 0.1 , A200 8.1 ± 1.9 to 2.3 ± 0.4 .

Ratios of β_1 : β_2 -adrenoceptor antagonism were also calculated to provide an index of β_1 -adrenoceptor selectivity (Table 2). This showed that increasing doses of betaxolol were associated with a progressive reduction in the degree of selective β_1 -adrenoceptor blockade, and that this is unchanged after 24 h compared with peak effects. The 200 mg dose of atenolol was less β_1 -selective at its peak compared with the 50 mg dose. However, after 24 h the ratios for β_1 : β_2 -adrenoceptor blockade were comparatively reversed due to the relatively greater decline in β_2 - and β_1 -adrenoceptor antagonism with A200 and A50 respectively.

Discussion

A thorough understanding of β -adrenoceptor subtypes involved in mediating responses to isoprenaline and exercise is required in order to interpret the findings of the present study. The effect of maximal exercise on heart rate is generally considered to be the best available method of evaluating β_1 -receptor antagonism (McDevitt, 1977, 1989). Exercise-induced tachycardia is due to a combination of noradrenergic cardiac sym-

pathetic stimulation and inhibition of cardiac vagal tone. The absence of a significant effect of ICI 118,551 (β_2 -adrenoceptor selective antagonist) on exercise heart rate is also consistent with the model of β_1 -adrenoceptor stimulation (Pringle *et al.*, 1988). The resting heart rate is mainly dependent on vagal tone, and should therefore not be used to quantify β_1 -adrenoceptor blockade, since changes are of small magnitude (McDevitt *et al.*, 1977). The effects of isoprenaline on finger tremor are mediated by β_2 -adrenoceptors (Arnold *et al.*, 1984; Perucca *et al.*, 1981; Pringle *et al.*, 1988), whereas effects on heart rate and diastolic blood pressure are generated by a combination of β_1 - and β_2 -adrenoceptors (Pringle *et al.*, 1988). In addition to direct stimulation of cardiac β_1 - and β_2 -adrenoceptors (Arnold *et al.*, 1985; Brown *et al.*, 1986; Corea *et al.*, 1984; Strauss *et al.*, 1986), isoprenaline also produces a decrease or increase in cardiac vagal tone, depending on whether administration is by bolus injection or infusion respectively (Arnold & McDevitt, 1986). Thus, for the purposes of this discussion the relative antagonism of β_1 - and β_2 -adrenoceptors will be based upon the attenuation of exercise heart rate and isoprenaline-induced finger tremor.

Our results showed that betaxolol and atenolol caused dose-related antagonism of β_1 -adrenoceptors, although there was a ceiling in effect above the 40 mg dose of betaxolol. A pharmacokinetic explanation is not tenable since there were appropriate two-fold increments in plasma concentrations between 40 mg and 80 mg doses of betaxolol. McDevitt and co-workers (1977) showed that a ceiling in effect on exercise heart rate occurs with drugs which possess intrinsic sympathomimetic activity (ISA) such as practolol and oxprenolol, but this does not occur with atenolol or sotalol which are devoid of ISA. Thus, a possible explanation might be that betaxolol possesses partial β_1 -adrenoceptor agonist activity at higher than conventional doses (10–40 mg), or alternatively that maximal obtainable β_1 -adrenoceptor blockade occurs with the 40 mg dose.

There were comparable reductions in exercise heart rate after 24 h between atenolol 50 mg and betaxolol 10 mg, and between atenolol 200 mg and betaxolol 40 mg. This is surprising in view of the known difference in pharmacokinetic half-lives between atenolol (6 h) and betaxolol (14 h) (Balnave *et al.*, 1981; Brown *et al.*, 1976; Cadigan *et al.*, 1980; Fitzgerald *et al.*, 1978; Warrington *et al.*, 1980). In a previous single-dosing study (Balnave *et al.*, 1981), there was a significantly greater reduction in exercise tachycardia 24 h after administration of betaxolol 40 mg in comparison with atenolol 200 mg. In a chronic dosing study comparing atenolol 200 mg once daily vs atenolol 100 mg twice daily, the latter regime was associated with higher blood levels and greater reduction of exercise heart rate prior to the morning dose, whereas differences were less marked at 3 h after the morning dose (Brown *et al.*, 1976).

There were also similar dose-dependent increases in antagonism of β_2 -adrenoceptors. Doses of atenolol (200 mg) and betaxolol (40 mg) which produced equivalent β_1 -adrenoceptor blockade also caused equal antagonism of β_2 -adrenoceptors at peak effect, and can therefore be said to possess similar degrees of

Table 2 Ratios of β_1 : β_2 -adrenoceptor antagonism at peak and trough

	B10	B40	B80	A50	A200
Peak	7.7	5.8	4.5	10.5	6.1
Trough	8.5	6.2	4.0	7.6	8.8

Ratios for β_1 : β_2 -adrenoceptor blockade were calculated as: % reduction exercise heart rate $\div$ IT₁₀₀ dose-ratio, for peak (2–4 h) and trough (24 h) values.

β_1 -adrenoceptor selectivity. After a period of 24 h, despite similar β_1 -adrenoceptor blockade, atenolol 200 mg showed a proportionally greater decline in β_2 -adrenoceptor blockade compared with betaxolol 40 mg (Table 1). Thus the 200 mg dose of atenolol exhibited a relative increase in β_1 -adrenoceptor selectivity over the 24 h period of time (Table 2). The decline in β_2 -adrenoceptor blockade (from peak to trough) was least for betaxolol 80 mg (Table 1), and hence the low ratio of selective β_1 -adrenoceptor blockade persisted after 24 h (Table 2). It was also of interest to find that the β_1 -adrenoceptor selectivity ratios for both doses of atenolol were comparatively reversed after 24 h, due to the relatively greater declines in β_2 - and β_1 -adrenoceptor blockade with 200 mg and 50 mg doses respectively. Previous comparative studies have shown that the β_1 -adrenoceptor selectivity of betaxolol is similar to that of atenolol, metoprolol and practolol, but much greater than that of propranolol (Pringle *et al.*, 1987; Riddell & Shanks, 1985; Saunders *et al.*, 1981). Furthermore, even higher than conventional doses of atenolol and betaxolol produce significantly less β_2 -adrenoceptor blockade in comparison with propranolol (Irvine *et al.*, 1990; Lipworth *et al.*, 1989a).

It would therefore appear that once daily treatment with atenolol 200 mg and betaxolol 40 mg provides effective antagonism of β_1 -adrenoceptors over a 24 h period, but at the expense of a relatively high degree of β_2 -adrenoceptor blockade. However, the latter appears to wear off to a greater degree with the high dose of atenolol. The lower doses of atenolol (50 mg) and betaxolol (10 mg) caused significant β_1 -adrenoceptor blockade for up to 8 h as well as negligible antagonism of β_2 -adrenoceptors. These findings infer that the use of a lower twice daily dose of betaxolol or atenolol might be of greater benefit than a larger once daily dose in providing effective β_1 -adrenoceptor blockade over a 24 h period, without causing significant antagonism of β_2 -adrenoceptors. Further studies are now indicated to assess whether this type of regime might be more preferable for patients with angina pectoris who have coexistent airflow obstruction or peripheral vascular disease.

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