Comparison of the cardiovascular and pulmonary effects of oral celiprolol, propranolol and placebo in normal volunteers

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- 1 The effects on heart rate, blood pressure and pulmonary function of single oral doses of celiprolol hydrochloride (400 mg), and propranolol (40 mg) were compared with placebo in 12 healthy volunteers, in a double-blind three-period crossover study.
- 2 Celiprolol had no effect on heart rate while propranolol caused a significant reduction compared with placebo. Systolic blood pressure was reduced by propranolol but not celiprolol, whereas standing diastolic blood pressure was lowered by both drugs.
- 3 The maximal expiratory flow at 50% vital capacity (MEF₅₀), was significantly lower after propranolol compared with placebo and celiprolol. Celiprolol had no effect on the flow-volume loop parameters.
- 4 Effective pulmonary blood flow was significantly increased by celiprolol, but reduced by propranolol.
- 5 A high incidence of subjective side-effects were experienced on celiprolol (10/12; particularly unpleasant in 5). Side-effects were experienced to a lesser extent on placebo (8/12). Only one volunteer experienced a side-effect on propranolol.
- 6 Oral celiprolol exerts its hypotensive effect by vasodilatation without reflex tachycardia. It does not cause airways obstruction in healthy subjects.

Keywords vasodilator agents β -adrenoceptor blockers pulmonary circulation

Introduction

Celiprolol hydrochloride, 3-[3-acetyl-(3-(tert-butylamino)-2-hydroxypropoxy)phenyl]-1,1-diethylurea hydrochloride, is a β_1 -selective adrenoceptor blocker with partial β_1 - and β_2 -adrenoceptor agonist activity, and weak α -adrenoceptor antagonist properties (Riddell *et al.*, 1987). This combination may lead to cardio-selective β_1 -adrenoceptor blockade, without the usual disadvantages of β_2 -adrenoceptor blockade, namely bronchoconstriction, depression of left ventricular function and peripheral vasoconstriction. The aim of this study was to compare the effects of oral celiprolol (400 mg), propranolol (40 mg) and placebo on cardiopulmonary function in normal subjects. It was thought unethical to use subjects with airflow

obstruction or cardiac failure in such a study, as major side-effects have been reported in these groups following administration of other β -adrenoceptor blockers.

Methods

Twelve normal healthy volunteers were studied. There were seven males, and the group mean age was 30 years, range 23–35 years. All were lifelong non-smokers, and none gave a history of major or recent minor cardiorespiratory disease. Full physical examination, 12 lead electrocardiogram (ECG), PA chest radiograph, spirometry, full blood count, urea, electrolytes,

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liver function tests and urinalysis were performed. No medication which might affect the cardiorespiratory system was taken in the 2 months prior to the study. All gave informed consent and the protocols were approved by the Brompton Hospital Ethics committee.

The study was conducted under placebo controlled, double-blind, crossover conditions, each subject receiving all three study treatments after being randomised to one of six possible treatment sequences. Each subject was investigated on four separate occasions at least 7 days apart. On the first occasion, a rehearsal day, no drugs were given to the subject; otherwise the identical protocol was followed on each occasion. Each study day was preceded by an overnight fast. No alcohol or caffeinated drinks were permitted during any study day.

The subjects came to the laboratory, and the pre-treatment (-1 h) measurements were made, (see below). The appropriate test medication was then swallowed with 150 ml of water (0 h). There was a 1 h break, and then the measurements were repeated hourly for the next 6 h. A standard light breakfast was consumed 2 h after dosing, and a standard lunch 3 h after dosing. Free clear fluids were permitted from 3 h after dosing. Each hour, the same measurements were made in the identical order, as follows:

(a) Sitting and standing radial pulse and blood pressure were determined by the oscillometric method using an automatic, non-invasive, blood pressure monitor, with the cuff placed around the upper arm and the cuff bladder placed over the brachial artery (Dinamap vital signs monitor, Critikon Ltd, USA). There is good agreement between oscillometrically measured blood pressure and central aortic pressure measured invasively (Borow & Newburger, 1982). Measurements were taken on each occasion after the subjects had been sitting for 5 and standing for 2 min, and the mean of three reproducible readings was taken.

(b) Three reproducible maximal flow-volume loops were then obtained using the Floop ITM pulmonary function studies system (Oldelft). The following indices of ventilatory function were derived:

- (1) forced expired volume in 1s (FEV_1), forced vital capacity (FVC), and FEV_1/FVC %.
- (2) peak inspiratory and expiratory flow rates (PIFR and PEFR)
- (3) maximal expiratory flow at 75% (MEF.75), 50% (MEF.50) and 25% (MEF.25) of vital capacity remaining.

(c) Accessible lung volume (VA) and effective

pulmonary blood flow (EPBF) were measured by the single breath argon/freon test (Denison *et al.*, 1980; Denison & Waller, 1982). In this technique the subjects, who had been seated at rest for 10 min, inspired a vital capacity of a test gas containing 10% argon, 3.5% freon-22 (chlorodifluoromethane), 35% oxygen in nitrogen. After a 1–2 s breath-hold at total lung capacity, they then exhaled slowly to residual volume at a rate of 0.08 l s^{-1} . The changing partial pressures of argon and freon-22 were monitored at the lips by a mass spectrometer (MGA 200, Centronics Ltd) and plotted against time on a flat bed, four channel pen recorder (Linseis Ltd). Seven such manoeuvres were performed at 3.5 min intervals and the last five of the traces obtained were analysed. The traces were digitised on a Tektronix tablet, linked via a graphics terminal to the hospital mainframe computer (Prime 750). The calculations were as described elsewhere (Denison *et al.*, 1980). The dilution volume of argon, VA, is within six sevenths of total lung capacity as measured in a body plethysmograph in our laboratory. That part of pulmonary blood flow which takes part in gas exchange, EPBF, is within 95% of cardiac output in normal people (Davidson *et al.*, 1972). EPBF was measured from the time constant of the fall in the partial pressure of freon-22 between a previously fixed time interval (usually 10–20 s from the start of the manoeuvre), because a previous study had shown that this yielded more reproducible results than selecting a linear portion by eye (Bush *et al.*, 1988). The mean within study coefficient of variation ($100 \times \text{s.d./mean}$) of EPBF has been shown to be 5.5% (Bush *et al.*, 1988). The between study mean coefficient of variation of EPBF has been shown to be 6.5% (Waller, 1982).

Three hours after dosing, 20 ml of blood was removed by antecubital fossa venepuncture for assay of drug levels. The blood was collected into heparinised bottles, and immediately spun at $2000 \text{ rev min}^{-1}$ in a centrifuge for 10 min. The supernatant plasma was removed with a clean pipette, and frozen at -20°C in a glass tube prior to analysis at the end of the study. Plasma drug levels were measured using high pressure liquid chromatography with chloroform extraction and ultraviolet absorption.

At the end of each study day, the answer to the question 'Have the study tablets upset you in any way?' was noted. Routine safety checks, including a full physical examination, ECG, haematology and urinalysis were made within 72 h of the final study day for each subject.

The statistical analysis was performed with the Statistical Analysis System (SAS) version 6.0

computer software package, (SAS Institute Inc.). The main efficacy analyses of respiratory and cardiovascular function were made on the 1 h post-dose (1 h) measurement (immediate response), the mean of 1–3 h (principal response) for the time between dose and plasma concentration measurement, and the mean of all 6 h (overall response). Baseline (predose, –1 h) for each day was subtracted from the post-dose measurements for that day, so that differences from baseline were analysed. Each measurement was analysed with a linear model for crossover design. This method permits direct comparison of treatments with adjustment of effects applicable to the crossover design of the study, namely patient effects, visit effects and carryover effects. The latter two effects did not prove significant. The linear analyses were based on linear model methods (Neter *et al.*, 1985) using the GLM procedure in SAS. The linear model analyses assume normal distributions of the dependent variables; this assumption was tested and found to be valid.

Results

The data for the rehearsal day (day 1, no treatment) are not presented. Comparisons are between the three treatment days (placebo, celiprolol, propranolol). There were only minor differences between the baseline measurements made prior to dosing on each of the treatment days. The day on which the subjects were about to take propranolol differed significantly ($P < 0.05$) from the day on which they were about to take placebo for PIFR (mean $\pm$ s.d. = 6.5 ± 1.8 vs 7.1 ± 2.1 l s⁻¹), MEF.50 (4.2 ± 1.2 vs 3.9 ± 1.0 l s⁻¹) and EPBF (4.73 ± 0.97 vs 5.02 ± 1.04). There were no significant differences between either the celiprolol and propranolol days or the celiprolol and placebo days. This modest amount of baseline heterogeneity probably arose by chance. In any case, baseline variability is allowed for by the subtraction of baseline from post-dose values in the analysis.

Respiratory variables

There were no statistically significant differences between the three treatments for FEV₁ and FVC, nor between celiprolol and placebo for any respiratory variable in the three responses (immediate, principal, overall). There were trends towards smaller means on propranolol compared with those on celiprolol and placebo for FEV₁ (overall response mean difference being 0.08 l, $P = 0.057$, and 0.08 l, $P = 0.059$

respectively), and for propranolol vs placebo for FVC (principal response mean difference being 0.08 l, $P = 0.059$). Both the principal and the overall response for MEF.50 were significantly lower on propranolol compared with celiprolol (0.44 l s⁻¹, $P = 0.011$, and 0.50 l s⁻¹, $P = 0.003$ respectively), with the immediate response showing a trend for a lower MEF.50 (0.32 l s⁻¹, $P = 0.052$). The overall response for MEF.50 was significantly lower for propranolol compared with placebo (0.33 l s⁻¹, $P = 0.041$). There were no differences between any of the study days for VA.

Cardiovascular variables

Celiprolol had no significant effect on heart rate sitting or standing, but propranolol, as expected, resulted in significant reductions in both postures for immediate, principal and overall analyses. Propranolol caused significant reductions in systolic blood pressure for both postures in all three analyses; celiprolol had no effect on this measurement in any of the analyses. Neither

Figure 1 Changes in systolic and diastolic blood pressure and heart rate, measured while seated (respectively SBP, DBP, HR). ● placebo; ▲ propranolol; ■ celiprolol. The mean and s.e. mean is shown for each point. Propranolol causes falls in SBP and HR compared with placebo and celiprolol.

Figure 2 Changes in systolic and diastolic blood pressure and heart rate, measured while standing (respectively SBP, DBP, HR). ● placebo; ▲ propranolol; ■ celiprolol. The mean and s.e. mean is shown for each point. Propranolol causes falls in HR, SBP and DBP; celiprolol causes a fall in DBP only.

Figure 3 Changes in effective pulmonary blood flow (EPBF). ● placebo; ▲ propranolol; ■ celiprolol. The mean and s.e. mean is shown for each point. Celiprolol causes a rise in EPBF, while propranolol causes a fall compared with placebo.

drug significantly altered diastolic blood pressure in the sitting position. In the standing position, there were no significant differences between the two drugs in any of the three analyses; both caused significant reductions in diastolic blood pressure compared with placebo (Figures 1 and 2), except in the immediate response, when there was no difference between celiprolol and placebo.

Celiprolol and propranolol had markedly different effects on EPBF (Figure 3). The immediate response to celiprolol was an increase in EPBF compared with both propranolol and placebo (change over baseline 0.63 ± 0.77 vs -0.74 ± 0.59 vs -0.32 ± 0.39 l min⁻¹ respectively; no significant difference was shown between placebo and propranolol). In the principal and overall response the mean EPBF was significantly increased on celiprolol and reduced on propranolol, compared with placebo (principal response, 1.17 ± 0.65 vs -0.14 ± 0.52 vs 0.39 ± 0.30 ; overall response, 1.20 ± 0.59 vs 0.05 ± 0.45 vs 0.46 ± 0.34 , respectively for celiprolol, propranolol and placebo; all differences, $P < 0.05$).

Plasma drug concentrations

Mean $\pm$ s.d. concentration of celiprolol was 2962 ± 1133 ng ml⁻¹, range 1747–5562. One subject's concentration (5562) was considerably greater than the others; this skews the results, and if it is omitted, the levels are 2702 ± 775 ng ml⁻¹, range 1747–3806. For propranolol, the mean $\pm$ s.d. concentrations were 29.5 ± 15.5 , range 12.4 to 58.7.

Adverse effects

All the safety checks listed above were normal before and after the study. When treated with celiprolol, only two subjects did not experience side-effects. In the other ten, the main complaint was 'shakiness', feeling very cold despite being in a warm room, and feeling generally unwell. In five these symptoms were particularly unpleasant, and four spontaneously volunteered that the symptoms persisted into the evening. In addition, three had headaches, and five actually fell asleep in between tests. On placebo, eight subjects had side-effects. These were headaches (four subjects, persisting into the evening in three); three felt sleepy, two of whom fell asleep between tests; and two complained of either nausea, feeling cold, or lightheadedness. On propranolol, one subject had a headache; there were no other side-effects.

Discussion

The main conclusions of this study are that in normal people celiprolol has no effects on lung function, but reduces diastolic blood pressure while increasing EPBF. By comparison, propranolol causes airflow obstruction even in normal subjects, and also bradycardia and reductions in systolic and diastolic blood pressure, while not altering pulmonary blood flow.

The effect of β_2 -adrenoceptor blockade on lung function in normal subjects is variable (Kumana *et al.*, 1974). Propranolol has been reported by some to increase airways resistance and reduce FEV₁ and PEFR (McNeil & Ingram, 1966; Stone *et al.*, 1973), while other workers have failed to confirm this (Singh *et al.*, 1976). Both oral metoprolol and atenolol have been shown significantly to reduce FEV₁ in normal subjects (Johnson & Clarke, 1978). We showed that propranolol predominantly reduced MEF₅₀, with no significant change in MEF₂₅ or VA, suggesting that large airway bronchoconstriction was responsible. Possibly the effects on FEV₁ or FVC might have been significant if we had used a larger dose of propranolol. By contrast, celiprolol had no effects on the flow volume loop. There is some evidence in animals (Gordon *et al.*, 1982) and asthmatic patients (Doshan *et al.*, 1986) that celiprolol may even be a bronchodilator. It does not antagonise the bronchodilator effects of β_2 -adrenoceptor agonists or aminophylline (Matthys, 1982). Despite this, celiprolol should be used only with extreme caution in asthmatic patients. Some asthmatics have reported an increased incidence of acute attacks on celiprolol (Capone *et al.*, 1985) with an increased airways resistance (Kaik, 1980); and even small doses of other 'cardioselective' β -adrenoceptor blockers have caused bronchoconstriction (Formgren, 1976; Lofdahl & Svedmyr, 1981). The widespread use of celiprolol, rather than less selective β -adrenoceptor blockers, might reduce the morbidity and mortality of the inadvertent prescription of β -adrenoceptor blockers to asthmatics (Fraunfelder & Barker, 1984).

Propranolol, in common with other non-selective β -adrenoceptor blockers, is well known to impair left ventricular function. By contrast, celiprolol increased myocardial contractility in anaesthetised dogs (Shlevin *et al.*, 1983) and increased forearm bloodflow in hypertensive patients (Mancia *et al.*, 1986). We have shown that celiprolol caused significant in-

creases in EPBF, which is close to cardiac output in normal subjects (Davidson *et al.*, 1972), whereas propranolol depressed EPBF. This suggests that celiprolol may be a safer drug when left ventricular function is already compromised, and a further fall in cardiac output would be dangerous. As expected, propranolol caused bradycardia, and falls in systolic and diastolic blood pressure. Our data showed that celiprolol had an equal effect on diastolic blood pressure, but no effect on heart rate or systolic blood pressure. The absence of an effect on systolic blood pressure could be a disadvantage, since systolic as well as diastolic hypertension is now recognised as a risk factor for cerebrovascular accident (Kannel *et al.*, 1981).

A disturbingly high incidence of side-effects was found with celiprolol (10/12), and to a lesser extent with placebo (8/12). Somnolence and headache were common to both in varying degrees. The feeling of cold in a warm environment (temperature 24 to 26 °C) experienced by 8/12 subjects while on celiprolol, was very marked. This side-effect has not been reported before to our knowledge and its mechanism is unknown. The plasma drug concentrations were higher than previously reported (Caruso *et al.*, 1985; Norris *et al.*, 1986), but lower than those produced by 600 mg celiprolol, a dose which is well tolerated (Caruso *et al.*, 1985). High drug levels therefore seem unlikely to be a factor. Side-effects have not been reported as a major problem in previous larger studies (Niederberger *et al.*, 1983; Hoffman & Hoffman, 1986), but in our small group they were sufficiently unpleasant that 5/12 subjects would have been unwilling to tolerate the drug longterm.

In conclusion, this study suggests that celiprolol may be devoid of the bronchoconstrictor and negative inotropic effects of propranolol. From our data any possible therapeutic role of celiprolol must remain speculative, particularly in view of the high incidence of side-effects that we encountered in normal subjects. Provided a satisfactory alternative was available, no β -adrenoceptor blocker would ever be prescribed to patients with reversible airflow obstruction or incipient left ventricular failure, because of the risk of deterioration in these conditions. Nevertheless, when β -adrenoceptor blockade is the preferred treatment of first choice, it is possible that celiprolol may offer significant advantages over propranolol in patients at risk from the unwanted cardiovascular and pulmonary side-effects of β_2 -adrenoceptor blockade.

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