Effect of CGP 17/582, a selective β -adrenoceptor antagonist, on the haemodynamic and hypokalaemic response to adrenaline

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1 CGP 17/582B is a new β -adrenoceptor antagonist which on experimental studies appears to combine selective β_1 -adrenoceptor blockade with partial agonist activity (ISA). Assessing β -adrenoceptor selectivity and the degree of partial agonist activity *in vivo* can be difficult.

2 In a double-blind placebo controlled crossover study we have compared the effect of oral pretreatment for 7 days with CGP (100 mg twice daily), with propranolol (non-selective β -adrenoceptor blocker with no ISA) and metoprolol (selective β -adrenoceptor blocker with no ISA) on resting heart rate and heart rate response to submaximal exercise on a bicycle ergometer to assess the degree of β -adrenoceptor blockade and also the changes in blood pressure, heart rate and potassium during the intravenous infusion of (–)-adrenaline to determine the degree of β_2 -adrenoceptor blockade.

3 Subjects underwent submaximal exercise testing on the second and fifth day of each treatment period and on the seventh day received a 2 h infusion of (–)-adrenaline ($0.06 \mu\text{g kg}^{-1} \text{min}^{-1}$). Heart rate, blood pressure, plasma potassium and catecholamines were measured throughout the study period.

4 All three active treatments significantly reduced exercise induced tachycardia. The (–)-adrenaline infusion significantly reduced plasma noradrenaline levels following propranolol and metoprolol and to a lesser extent with placebo but were unaltered on CGP. Baseline heart rate was unaltered by CGP but was significantly reduced by metoprolol and propranolol. Adrenaline significantly reduced plasma potassium levels following placebo and CGP pretreatment but plasma potassium was unaltered by adrenaline with metoprolol and propranolol pretreatment.

5 The results of this study confirm that CGP is a selective β_1 -adrenoceptor antagonist in man. The failure of the (–)-adrenaline infusion to inhibit noradrenaline release during CGP treatment is supportive evidence for the existence of a β_2 -presynaptic receptor facilitating noradrenaline release.

Keywords β -adrenoceptor blockade selectivity adrenaline noradrenaline hypokalaemia

Introduction

CGP 17/582B is a β -adrenoceptor antagonist (Figure 1) which on experimental studies appears to combine β_1 -adrenoceptor blocking selectivity with partial agonist activity or in-

trinsic sympathomimetic activity (ISA). This combination of pharmacological properties is different from any of the currently available β -adrenoceptor antagonists, other than practolol.

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Figure 1 Chemical formula and structure of CGP 17582B.

The assessment of β -adrenoceptor selectivity is difficult *in vivo* (McDevitt, 1977) and there have been discrepancies between radioligand binding studies and clinical studies (Weiner, 1985) and between animal and clinical studies (Barrett *et al.* 1973; Marlin *et al.*, 1975) with β -adrenoceptor blockers in the past.

β -adrenoceptor blockade can be investigated by measuring the chronotropic, vasopressor and respiratory function changes following intravenous isoprenaline (Cleaveland *et al.*, 1972; Thiringer & Svedmyr, 1976). However doubts have been raised as to the reliability of this method (McDevitt, 1977). More recently other methods have been proposed (McDevitt, 1977; Arnold & McDevitt 1983a) including examining the effect of β -adrenoceptor antagonists on β -adrenoceptor agonist induced hypokalaemia (Smith *et al.*, 1983, Struthers *et al.*, 1983a; Vincent *et al.*, 1984). Adrenaline induced hypokalaemia is mediated by β_2 -adrenoceptors (Struthers & Reid, 1984a; Brown *et al.*, 1983).

The aim of this study was to examine the effect of CGP 17582B, a β -adrenoceptor-antagonist claimed to be highly selective for the β_1 -adrenoceptor, on the hypokalaemic and haemodynamic effects of a (-)-adrenaline infusion. We have studied the effect of pretreatment for 7 days with oral CGP 17582B on heart rate in response to submaximal exercise on a bicycle ergometer and also the changes in blood pressure, heart rate and potassium during the intravenous infusion of (-)-adrenaline. To aid interpretation of the results in the same protocol the effects of treatment with propranolol (non-selective β -adrenoceptor blocker with no ISA) and metoprolol (selective β_1 -adrenoceptor blocker with no ISA) and an inactive placebo control were examined.

Methods

Eight healthy volunteer subjects (four females, four males; age 19–37 years; weight 51–67 kg) were studied after giving fully informed consent. The protocol of the study was approved by the

Research and Ethics Committee of the Greater Glasgow Health Board, Northern District. Subjects were on no regular drug therapy and had normal routine haematology, biochemistry and electrocardiograms.

This was a placebo controlled double-blind study with supplies being dispensed by the Hospital Pharmacy. Subjects received all four treatments in a randomised Latin square design order with at least 2 weeks between treatments to ensure adequate washout. All drugs were matched using a disguised gelatine capsule. The four treatments were i) placebo capsule twice daily; ii) propranolol 80 mg twice daily; iii) metoprolol 100 mg twice daily; iv) CGP 17582B 100 mg twice daily and each therapy was administered for 1 week. Prior to each treatment period and on the second and fifth day of each treatment subjects underwent a standard submaximal exercise test, 2 min of exercise at 100 watts min^{-1} , using a bicycle ergometer in order to confirm and compare the degree of β -adrenoceptor blockade achieved. Subjects attended the laboratory on the seventh day of each therapy having abstained from caffeine, food, alcohol and tobacco for 10 h.

A standard light breakfast was administered together with the drug and cannulae inserted into each forearm for withdrawal of plasma samples and the infusion respectively. Subjects were studied supine throughout and after 1 h a 5% (+)-glucose infusion, containing 1 mg ml^{-1} of ascorbic acid, was commenced at a rate of 12 ml h^{-1} via a Braun VI perfusor pump. Baseline plasma samples were taken for the measurement of plasma potassium and catecholamines and blood pressure and heart rate were also measured. These measurements were repeated at regular intervals throughout the study period as shown in the diagram illustrating the detailed study design (Figure 2). One hour after the start of the (+)-glucose vehicle an infusion containing (-)-adrenaline in (+)-glucose, also containing ascorbic acid, was commenced at a low dose infusion rate of 0.01 $\mu\text{g kg}^{-1} \text{min}^{-1}$. If after 10 min of infusion at this rate there were no adverse haemodynamic effects

Figure 2 Detailed outline of study day. Each study period was identical except for the pretreatment.

the infusion rate was increased to $0.02 \mu\text{g kg}^{-1} \text{min}^{-1}$ of (-)-adrenaline and the infusion rate was increased stepwise in this fashion to a maximum of $0.06 \mu\text{g kg}^{-1} \text{min}^{-1}$ if no adverse effects occurred. This rate was contained for 90 min during which blood pressure, heart rate and plasma potassium and catecholamine levels were measured (Figure 2). Following the (-)-adrenaline infusion the (+)-glucose vehicle infusion was continued for a further 2 h and the measurements repeated during the recovery period.

Systolic and diastolic blood pressure were measured in duplicate by a semi-automated sphygmomanometer (Sentron, Bard Medical Division, Lombard, Illinois). Heart rate was counted at the radial artery by palpation for 30 s. An electrocardiogram was displayed continuously throughout the study period.

Plasma potassium samples were collected into lithium heparin tubes and centrifuged within 30 min of collection at 4°C . Samples were analysed by a Technicon SMA-C autoanalyser (Technicon Instrument Co., New York, U.S.A.) using standard flame photometry methods.

Plasma samples for catecholamine assay were collected into chilled lithium heparin tubes and centrifuged within 15 min at 4°C and then stored at -70°C prior to assay. A high performance liquid chromatography assay (h.p.l.c.) was used with a coefficient of variation of 5–10% and a limit of detection of 0.1 nmol l^{-1} for both adrenaline and noradrenaline. The system was a paired ion reverse phase (h.p.l.c.) system with an electrochemical detector with a mobile phase

containing phosphate buffer and octyl sulphonic acid as the paired ion reagent. A $5 \mu\text{m}$ ODS column was employed with 3,4 dihydroxy benzolamine hydrobromide as the internal standard (Howes *et al.*, 1985).

Results are expressed as mean $\pm$ s.d. A repeated measures analysis of variance (ANOVA) computer modelling package was used for comparisons between treatments. Measurements before and after a manoeuvre (adrenaline infusion, exercise, etc.) were compared using a paired Student's *t*-test. Significance values were taken as $P < 0.05$ (Winer, 1971; Bryce, 1980).

Results

No subjects reported any side effects during the period β -adrenoceptor antagonists were given. There were no withdrawals. During the adrenaline infusion two subjects were aware of an increase in their heart rate on all treatments but no reduction in infusion rate was necessary.

Effect of β -adrenoceptor antagonists at rest and after exercise

These are shown in Table 1 and there was no difference in pretreatment baseline heart rates between treatment periods. Following 5 days of placebo there was no change in the tachycardia after 2 min exercise at $100 \text{ watts min}^{-1}$ (129 ± 17 beats min^{-1} on day 0 and 125 ± 24 on day 5). All active β -adrenoceptor blocker treatments significantly reduced exercise induced tachycardia,

Table 1 Post-exercise heart rate (mean $\pm$ s.d.) following 2 min dynamic exercise on a bicycle ergometer at 100 watts min^{-1} ($n = 8$, P values refer to comparison of heart rate at end of exercise period prior to therapy and heart rate at the end of exercise on day 5 of each treatment, N.S.D. = no significant difference)

Treatment	Heart rate (beats min^{-1})	
	Prior to therapy	Day 5 of therapy
Placebo	129 $\pm$ 17	125 $\pm$ 24
CGP 17/582B	131 $\pm$ 9	N.S.D.
Metoprolol	129 $\pm$ 16	$P < 0.01$
Propranolol	115 $\pm$ 15	$P < 0.01$
		$P < 0.05$

metoprolol from 129 $\pm$ 16 to 88 $\pm$ 8 (32% inhibition), ($P < 0.001$); CGP 17/582B from 131 $\pm$ 9 to 99 $\pm$ 16, (24% inhibition), $P < 0.01$ and propranolol from 115 $\pm$ 15 to 93 $\pm$ 22, (19% inhibition) ($P < 0.05$), confirming β -adrenoceptor blockade after all three active treatments.

Plasma catecholamine concentrations

The plasma adrenaline concentrations prior to the (–)-adrenaline infusions were not significantly different between placebo and any of the three β -adrenoceptor antagonists (see Table 2). Following (–)-adrenaline administration the adrenaline levels were comparable to previous studies (Struthers & Reid, 1984a; Brown *et al.*, 1983) with a 30 fold increase over baseline values being observed. There were no significant differences in the adrenaline concentrations throughout the infusion period between treatments compared with placebo. As the infusion rate was the same in all studies this suggests that adrenaline clearance was not altered by any of the β -adrenoceptor antagonists used in the

study. The baseline plasma noradrenaline levels were not different after 7 days therapy with any of the β -adrenoceptor antagonists. However, noradrenaline levels decreased significantly during the (–)-adrenaline infusion on the placebo, metoprolol and propranolol study days but not following CGP 17/582B (Table 2).

Effect of (–)-adrenaline infusion on blood pressure and heart rate

Changes in heart rate, systolic and diastolic blood pressure are shown in Figure 3. The resting heart rate was significantly reduced, compared with the placebo study day (68 $\pm$ 9 beats min^{-1}), by metoprolol to 54 $\pm$ 4 ($P < 0.01$) and by propranolol to 58 $\pm$ 4 ($P < 0.01$) but not by CGP 17/582B, 66 $\pm$ 6. The difference in heart rates remained throughout the study day and a rise in heart rate following (–)-adrenaline was not seen with either metoprolol or propranolol whereas maximum heart rates of 82 $\pm$ 10 beats min^{-1} and 77 $\pm$ 8 were observed with placebo and CGP 17/582B respectively. Correcting for

Table 2 Plasma adrenaline and noradrenaline levels prior to (120 min) and at the end (240 min) of the adrenaline infusion (mean $\pm$ s.d.; $n = 8$, P values refer to comparison between 120 min and 240 min; N.S.D. = no significant difference)

Treatment	Adrenaline concentration (nmol l^{-1})		Noradrenaline concentration (nmol l^{-1})	
	120 min	240 min	120 min	240 min
Placebo	0.2 $\pm$ 0.3	3.7 $\pm$ 1.4	2.1 $\pm$ 1.0	1.6 $\pm$ 0.6
CGP 17/582B	0.1 $\pm$ 0.2	4.0 $\pm$ 2.0	1.8 $\pm$ 0.7	1.8 $\pm$ 0.8
Metoprolol	0.1 $\pm$ 0.2	3.8 $\pm$ 0.5	2.3 $\pm$ 0.9	1.7 $\pm$ 0.7
Propranolol	0.05 $\pm$ 0.1	3.7 $\pm$ 2.2	2.5 $\pm$ 0.7	1.3 $\pm$ 0.4
				$P < 0.01$

Figure 3 Change in mean heart rate (upper panel) and blood pressure (lower panel) during the study period for each treatment, ●—● placebo; ○—○ CGP 17/582B; ▲—▲ metoprolol and △—△ propranolol. (* = $P < 0.05$, ANOVA compared with placebo).

differences in baseline measurements on the different study days demonstrates significant differences in heart rate between metoprolol and propranolol when compared with CGP 17/582B or placebo following the (–)-adrenaline infusion. At the end of the study, these changes in heart rate were still evident (Figure 3).

Systolic blood pressure was significantly reduced by metoprolol and propranolol when compared with placebo and CGP 17/582B. However when initial baseline differences were taken into account there were no significant differences in systolic blood pressure between treatments following the (–)-adrenaline infusion.

The initial diastolic blood pressure was significantly lower on propranolol (52 ± 6 mm Hg) compared with placebo (63 ± 6 mm Hg) and these differences were maintained with correction for baseline differences. After propranolol pretreatment there was a rise in diastolic pressure during the (–)-adrenaline infusion when compared with placebo ($P < 0.05$). The metoprolol group showed a modest difference from placebo throughout which was not significant when corrected for baseline differences ($P > 0.05$). On the CGP 17/582B study day changes in diastolic blood pressure after (–)-adrenaline did not differ significantly from the changes after adrenaline in the placebo pretreatment study day.

Plasma potassium

Changes in plasma potassium are shown in Figure 4. There were no significant effects of β -adrenoceptor blocker pretreatment. Following (–)-adrenaline infusion potassium fell significantly from 4.1 ± 0.3 to 3.5 ± 0.3 mmol l^{–1} when inactive placebo was used as pretreatment and a similar fall was seen on the CGP 17/582B study period from 4.0 ± 0.4 to 3.6 ± 0.3 mmol l^{–1}. A small but insignificant rise in plasma potassium was observed with propranolol (4.2 ± 0.3 to

4.3 ± 0.2 mmol l^{–1}). A small, insignificant fall occurred after metoprolol (4.1 ± 0.3 to 3.9 ± 0.3 mmol l^{–1}). One hour after the end of the (–)-adrenaline infusion plasma potassium was not significantly different in the four study periods.

Thus, the hypokalaemic response to adrenaline was significantly modified ($P < 0.05$, ANOVA) by both metoprolol and propranolol but was unaltered by CGP 17/582B when compared with placebo (Figure 4).

Discussion

β -adrenoceptor antagonists have wide uses in cardiovascular diseases and other areas of therapeutics. CGP 17/582B is an experimental β -adrenoceptor antagonist (Figure 1) which is thought to be highly selective for the β_1 -adrenoceptor and to possess intrinsic sympathomimetic activity (Klepzig & Strauer, 1986). Though its basic structure is a phenoxypropranolamine, common to most β -adrenoceptor blockers, it has two unusual features. The methoxy-ethoxy group is in the para position leading to cardioselectivity and mild intrinsic sympathomimetic activity and the amino-group has a salicylate moiety which may explain the

Figure 4 Change in mean plasma potassium ($n = 8$) during the study period for each treatment, ●—● placebo; ○—○ CGP 17/582B; ▲—▲ metoprolol and Δ—Δ propranolol. (* = $P < 0.05$, ANOVA compared with placebo).

very high receptor affinity of this compound (Figure 1).

While the clinical relevance of relative selectivity for the β_1 - or β_2 -subtypes of receptors (McDevitt, 1977; Weiner, 1985) and partial agonist or intrinsic sympathomimetic activity is still controversial (McDevitt *et al.*, 1977; Prichard *et al.*, 1980), it is of importance to be able to characterise these properties quantitatively as well as qualitatively in man. Unfortunately, some experimental approaches which are suitable for animal or *in vitro* studies are not readily applicable to studies *in vivo* in man. Radioligand binding studies while useful (Minneman *et al.*, 1979) give no functional information and white blood cells which offer an accessible tissue source in man are of the β_2 -subtype only (Galant *et al.*, 1978). In the past relative β_1 - and β_2 -selectivity has been assessed by infusing graded doses of isoprenaline and comparing the relative cardiac chronotropic responses (presumed to be β_1 -mediated) with the effects on diastolic blood pressure which are attributed to peripheral vascular β_2 -receptors (Briant *et al.*, 1973) and more recently to changes in respiratory function either at rest in asthmatic subjects (Thiringer & Svedmyr, 1976) or during severe exercise in normals (McDevitt, 1977). Unfortunately, human myocardium has a mixed population of β_1 - and β_2 -adrenoceptors; the assumptions based on chronotropic responses are thus not entirely valid (Carlsson *et al.*, 1972; McGibney *et al.*, 1983). In addition, the diastolic depressor responses to β_2 -adrenoceptor agonists involve a non- β_2 -adrenoceptor component which results from the vagal withdrawal and other reflex changes in autonomic outflow induced by the fall in blood pressure (Arnold & McDevitt, 1983b, c). Thus these methods of assessing relative selectivity are neither wholly reliable nor simple. It has been suggested that assessment of the hypokalaemic response to β -adrenoceptor agonist stimulation may be a useful *in vivo* method (Smith *et al.*, 1983).

The fall in potassium which follows adrenaline infusion is mediated by a membrane bound Na^+/K^+ ATPase linked to a β -adrenoceptor (Struthers & Reid, 1984a; Brown *et al.*, 1983). Several studies with β -adrenoceptor agonists and antagonists have suggested that the β -adrenoceptor is of the β_2 - subtype. This conclusion is drawn from the studies with selective agonists such as salbutamol (Vincent *et al.*, 1984; Whyte *et al.*, 1987a) and antagonists (Struthers *et al.*, 1983; Brown *et al.*, 1983; Struthers & Reid, 1984b) as well as with more direct studies in animals with radioligand binding techniques (Elfellah *et al.*, 1987). The non-selective β -

adrenoceptor blockers timolol, propranolol, oxprenolol and labetalol reverse adrenaline induced hyopkalaemia (Struthers *et al.*, 1983a, b; Whyte *et al.*, 1987b) while the relatively selective β_2 -antagonist ICI 118551 is particularly effective (Brown *et al.*, 1983; Struthers & Reid, 1984b). The selective β_1 -antagonists are less effective and atenolol only partially reversed the fall in potassium (Struthers *et al.*, 1983; Vincent *et al.*, 1984). The results of the present study with propranolol and metoprolol are consistent with these past findings. The haemodynamic and metabolic effects are in keeping with non-selective and relatively selective β_1 -adrenoceptor blockade respectively. CGP 17182B revealed a distinctive pattern. Although β -adrenoceptor blockade was observed with antagonism of exercise induced tachycardia comparable to the other active agents used, the response to adrenaline infusion was quite different. The fall in potassium and profile of blood pressure and heart rate changes were not different from placebo pretreatment. The persistent fall in potassium and diastolic blood pressure suggests that, at the dose used, blockade of β_2 -adrenoceptors in peripheral blood vessels and skeletal muscles is not apparent. The higher resting heart rate with CGP 17/582B compared with the other active agents suggests that a partial agonist or intrinsic sympathomimetic effect was present at this dose. However baseline plasma potassium was unchanged following CGP 17/582B suggesting that the degree of intrinsic sympathomimetic activity was insufficient to significantly stimulate the β_2 -adrenoceptor linked Na^+/K^+ ATP-ase.

Some groups have reported that β -adrenoceptor agonist infusion leads to increases in plasma noradrenaline due to stimulation of presynaptic facilitatory β_2 - adrenoceptors (Stjarne & Brundin, 1975; Yamaguchi *et al.*, 1977; Majewski *et al.*, 1980; Vincent *et al.*, 1982). Adrenaline, which has both β_2 - and α_2 -adrenoceptor agonist activity, decreased plasma noradrenaline in our study, confirming previous findings (Musgrave *et al.*, 1984). This could be due to a relative imbalance, at this dose of (-)-adrenaline, on the facilitatory β_2 - and inhibitory α_2 -adrenoceptor presynaptic mechanisms. After β -adrenoceptor blockade it might be expected that unopposed α_2 -adrenoceptor inhibitory action of adrenaline would lead to a fall in plasma noradrenaline. We did observe a larger fall in noradrenaline during the (-)-adrenaline infusion which was highly significant with propranolol and metoprolol pretreatment (Table 2). There was no significant effect on noradrenaline with CGP 17/582B. These

results would be at least consistent with the pharmacological role of presynaptic α - and β -adrenoceptors in man and suggest that the presynaptic receptor is indeed of the β_2 sub-type.

In man CGP 17/582B is a selective β -adrenoceptor antagonist with some partial agonist activity. We failed to demonstrate any evidence of selectivity following metoprolol, this may be the result of a combination of its relatively poor

selectivity and possibly to the dose of metoprolol being too high and not directly comparable. The haemodynamic profile of a drug such as CGP 17/582B may avoid pressor responses to adreno-medullary adrenaline released during smoking or other stress. However, such an agent may be less likely than a non-selective β -adrenoceptor blocker to maintain serum potassium during such stress.

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