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CAN THE BIOCHEMICAL RESPONSES TO A β_2-ADRENOCEPTOR STIMULANT BE USED TO ASSESS THE SELECTIVITY OF β-ADRENOCEPTOR BLOCKERS?

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The extent to which β-adrenoceptor blocking drugs counteract the biochemical responses to an infusion of terbutaline, a β_2-adrenoceptor agonist, has been investigated. In this study the β_1-selectivity of metoprolol was compared with the non-selective β-adrenoceptor blocker propranolol. The hypokalaemia produced by an infusion of terbutaline was reduced by low dose (50 mg) and high dose (200 mg) metoprolol and by low dose (40 mg) and high dose (160 mg) propranolol. The effects of propranolol on terbutaline induced hypokalaemia were more marked than those of metoprolol at both low dose ($P = 0.01$) and high dose ($P = 0.05$). Furthermore low dose metoprolol had less effect than high dose metoprolol ($P = 0.05$). The serum potassium appeared to rise slightly after propranolol. Low and high doses of both β-adrenoceptor blockers markedly reduced the terbutaline-induced hyperglycaemia, but the differences between the two drugs were not statistically significant.

Keywords β_2-adrenoceptor stimulation β-adrenoceptor blockade selectivity

Introduction

β_2-adrenoceptor agonists have been shown to influence a variety of biochemical parameters. An infusion of terbutaline produces a marked fall in serum potassium and rise in plasma glucose in normal volunteers (Kendall *et al.*, 1982). These changes in serum potassium and plasma glucose are thought to be mediated predominantly by β_2-adrenoceptors (Kendall, 1981; Petch *et al.*, 1981), and therefore should not be influenced by any loss of β_2 selectivity which has been suggested to occur when high doses of β_2-adrenoceptor agonists are used (Marlin & Turner, 1975).

In this study we report the influence of both a relatively β_1-selective and a non-selective β-adrenoceptor blocking agent upon these terbutaline-induced biochemical responses. Metoprolol was chosen as the selective drug and propranolol as the non-selective drug.

Methods

Subjects

Seven healthy male volunteers aged 19 to 23 years were studied. The nature and purpose of the study was explained to them and informed consent obtained. The study had been approved by the Central Birmingham Health District Research Ethical Committee. At their initial visit they underwent a clinical assessment and blood was taken for routine biochemical and haematological screening. No abnormalities were detected.

Methods

Volunteers attended on five separate occasions having fasted overnight. On arrival two intravenous cannulae were inserted, one into each forearm. One was used for blood sampling and the other for terbutaline infusion. Immediately after cannulation either placebo, metoprolol 50 or 200 mg, or propranolol 40 or 160 mg were given orally. The sequence of the five treatments was random. On each occasion basal blood samples were taken at 30, 40 and 50 min after cannulation. One hour after cannulation an intravenous infusion of terbutaline 500 μg was commenced using an IVAC 630 pump. This was set to deliver the entire dose at a constant rate over a period of 60 min. Blood samples were taken at 10 min intervals throughout the 1 h infusion period and at 30 min after completion of infusion. Throughout this period the subjects remained at rest.

Blood samples were analysed for plasma glucose concentration using an IL 919 analyser with glucose oxidase, phenol and 4-amino-phenazone. The potas-

sium was measured using an IL 543 flame photometer.

For each volunteer, mean basal values for serum potassium and plasma glucose were calculated from the three sets of basal recordings (taken 30, 40 and 50 min after cannulation). Subsequent results were expressed as increases or decreases in relation to the mean basal values for each individual. Statistical analysis of the results involved, (1) the use of three way cross classification analyses of variance, and (2) a study of orthogonal treatment contrasts. The three way analyses of variance were conducted separately on change in serum potassium and the change in plasma glucose. The three classifications used were subjects (7 levels), treatments (5 levels) and time of sampling (7 levels); the subjects were treated as random effects. The orthogonal contrasts were used to give detailed comparisons between the five treatments, such as high dose propranolol *vs* low dose propranolol, high dose metroprolol *vs* low dose metoprolol, etc. The subjects were again treated as random effects and thus 'error variance' was arranged to reflect subject to subject variability as well as analytical variability.

Results

The three basal values for both serum potassium and plasma glucose always yielded consistent results indicating that a satisfactory basal state had been reached. The mean absolute basal values and the mean changes (± s.e. mean) in serum potassium and plasma glucose at 20, 40, 60 and 90 min after starting the terbutaline infusion for each of the treatments are shown in Table 1.

Serum potassium

Terbutaline infusion alone produced a fall in serum potassium (maximum reduction of 0.89 mmol/l at the end of infusion). This response was lessened by both doses of both β-adrenoceptor blockers (Figure 1). Low dose propranolol produced a significantly greater reversal of terbutaline-induced hypokalaemia than low dose metoprolol ($P = 0.01$), and high dose propranolol produced a significantly greater reversal than high dose metoprolol ($P = 0.05$). High dose metoprolol produced a greater effect than low dose metoprolol ($P = 0.05$). There was no significant difference between the two doses of propranolol, the serum potassium appearing to rise slightly with these two treatments.

Plasma glucose

Following terbutaline infusion alone there was a rise in plasma glucose (maximum increase of 1.44 mmol/l at the end of infusion). This response was considerably lessened following β-adrenoceptor blockade with both doses of metoprolol and propranolol (Table 1). Although the rise in plasma glucose appeared to be more pronounced after low dose metoprolol than low dose propranolol, the difference was not statistically significant. Similarly there were no significant differences between high dose metoprolol and high dose propranolol, low and high dose propranolol, nor low and high dose metoprolol.

Discussion

The distinction between selective and non-selective

Table 1 Mean absolute basal values and changes in serum potassium and plasma glucose during an infusion of 500 μg of terbutaline under different conditions of β-adrenoceptor blockade (mean + s.e. mean).

	Mean absolute basal serum K^+	*Changes in serum potassium (mmol/l) (Time from beginning of terbutaline infusion (min))*				*Mean absolute basal glucose*	*Changes in plasma glucose (mmol) (Time from beginning of terbutaline infusion (min))*			
		20	*40*	*60*	*90*		*20*	*40*	*60*	*90*
Terbutaline alone (T)	4.21 ±0.14	−0.21 ±0.10	−0.72 ±0.12	−0.89 ±0.13	−0.70 ±0.11	4.53 ±0.07	0.34 ±0.05	1.10 ±0.20	1.44 ±0.23	1.28 ±0.25
T + metoprolol 50 mg	4.17 ±0.04	−0.03 ±0.05	−0.26 ±0.07	−0.36 ±0.06	−0.30 ±0.04	4.59 ±0.10	0.08 ±0.05	0.23 ±0.07	0.47 ±0.11	0.54 ±0.12
T + propranolol 40 mg	4.10 ±0.07	0.06 ±0.06	0.03 ±0.07	0.14 ±0.05	0.13 ±0.04	4.40 ±0.16	0.02 ±0.04	0.08 ±0.06	0.12 ±0.08	0.24 ±0.05
T + metoprolol 200 mg	4.18 ±0.07	0.07 ±0.07	−0.03 ±0.08	−0.01 ±0.06	−0.04 ±0.08	4.57 ±0.06	0.01 ±0.05	0.09 ±0.06	0.19 ±0.07	0.26 ±0.09
T + propranolol 160 mg	4.00 ±0.05	0.14 ±0.03	0.23 ±0.05	0.26 ±0.04	0.31 ±0.06	4.63 ±0.13	−0.06 ±0.06	−0.06 ±0.09	−0.04 ±0.07	−0.06 ±0.06

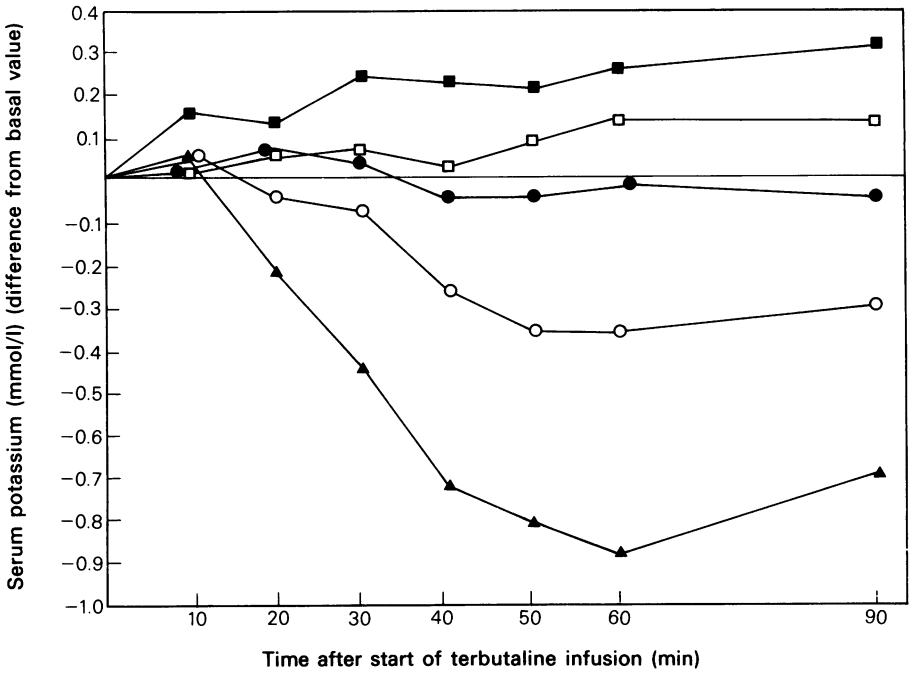

Figure 1 Mean change in serum potassium during an infusion of terbutaline (0–60 min) and at 90 min (n = 7; ▲ = placebo, 0 = metoprolol 50 mg, □ = propranolol 40 mg, ● = metoprolol 200 mg, ■ = propranolol 160 mg).

β-adrenoceptor blockers is clinically important. For example, the use of a selective β_1-adrenoceptor blocker is preferable in patients with airways obstruction, diabetes and peripheral vascular disease since these conditions may be exacerbated by β_2-adrenoceptor blockade (Kendall, 1981). However it is relatively difficult to obtain accurate and reproducible results from tests of respiratory function, and studies on the β-adrenoceptor blocking effects of drugs on airway patency performed on healthy volunteers are of doubtful relevance (Woods *et al.*, 1979). By comparison the measurement of serum concentrations of potassium and glucose are easy to perform, are relatively accurate and are universally available. Therefore these biochemical responses to a β_2-adrenoceptor stimulant have been examined as a means of assessing the selectivity of β-adrenoceptor blockade.

A fall in serum potassium and a rise in plasma glucose have been shown to occur in response to a variety of sympathetic stimuli (Phillips *et al.*, 1980; Leitch *et al.*, 1976; William-Olsson *et al.*, 1979), although the precise mechanisms are not fully understood. The fall in serum potassium may be due to a direct β_2-adrenoceptor mediated alteration in membrane permeability (Lockwood & Lum, 1974). Alternatively it may be secondary to an increase in insulin levels (Phillips *et al.*, 1980; William-Olsson *et al.*, 1979). Such a rise in insulin levels is seen in dogs following an infusion of salbutamol, a β_2-adrenoceptor agonist (Loubatieres *et al.*, 1971). This is not blocked by the β_1 specific blocker practolol whereas it is by the non-selective β-adrenoceptor blocker propranolol.

There is evidence to suggest that the rise in plasma glucose is due to gluconeogenesis and that this is β_2-adrenoceptor mediated (Kendall, 1981), although glycogenolysis following sympathetic stimulation may be α-adrenoceptor mediated (Lager *et al.*, 1979). The rise in insulin levels discussed above may to some extent reduce the β_2 mediated rise in blood sugar. It seems likely that the changes in serum potassium and plasma glucose produced by an infusion of terbutaline, are mediated mainly by β_2-adrenoceptors.

The results of this study suggest that modification of the hypokalaemic response, but probably not the hyperglycaemic response, to an infusion of terbutaline by β-adrenoceptor blockers may be used as a measure of selectivity. At both low and high doses, the selective β-adrenoceptor blocker metoprolol produced a significantly lesser effect on the serum potassium profiles than the non-selective β-adrenoceptor blocker propranolol. The doses of both β-adrenoceptor blockers used in this study were representative of the two extremes of the usual dose range. The

cause of the small rise in serum potassium after propranolol, which was more marked at the higher dose, is currently under study.

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