THE INHIBITION OF ADRENERGICALLY PROVOKED RENIN RELEASE BY SALBUTAMOL IN MAN

R. WIGGINS, R. DAVIES, I. BASAR & J.D.H. SLATER

Department of Medicine and the Cobbold Laboratories,
The Institute of Clinical Science, The Middlesex Hospital Medical School,
London, W.1

- 1 The β -adrenoceptor agonist salbutamol is shown to have antagonist properties by its effect on adrenergically provoked renin release in normal people.
- 2 It significantly reduces the rate of renin secretion provoked by either endogenous (85° head-up tilt) or exogenous (isoprenaline infusion) adrenergic stimulation.
- 3 Because renin is relatively simple to measure, and because in acute studies its release is relatively uninfluenced by the vagaries of direct and reflex cardiovascular effects, we suggest that, in the characterization of drugs which act on adrenergic β -receptors, an assessment of their effects on renin release would be useful.

Introduction

Renin release provoked by orthostasis and by isoprenaline infusion is mediated by activation of intrarenal β -adrenoceptors (Inoue, 1973; Sabto, Grunfeld & Moreau, 1975; Davies & Slater, 1976) and we have shown that an 85° tilt (Davies & Slater, 1976) and a low-dose isoprenaline infusion (Davies, Slater, Rudolf & Geddes, 1977) both give a highly reproducible and graded response in normal subjects. To characterize the adrenoceptor which mediates renin release, we have recently compared the effect of intravenous isoprenaline and salbutamol on plasma renin activity (PRA) in doses which produce similar haemodynamic effects (Davies, Geddes, Slater, Wiggins & Payne, 1975; Davies, Wiggins, Slater & Geddes, 1977). Although in the dose-ratio of isoprenaline to salbutamol 1 to 10, comparable agonist effects were seen when judged haemodynamically, isoprenaline provoked a brisk, dose-related release of renin, whereas salbutamol was without effect. Prompted by this lack of effect of salbutamol on renin release in resting supine subjects, we have set out to determine whether salbutamol has partial antagonist activity on adrenergically mediated renin release provoked by an 8 μ g isoprenaline infusion and by an 85° head-up tilt.

Methods

Four normal male volunteers aged 20–30 years participated. They were receiving no drugs and rested for 45 min before each study. Blood sampling was performed via a teflon cannula inserted into a left ante-cubital fossa vein. Blood was taken into cooled lithium heparin tubes, spun immediately and the plasma

stored at –20°. PRA was determined by an enzyme-kinetic technique and the generated angiotensin I was estimated by radioimmunoassay (Ménard & Catt, 1972). Arterial pressure was measured sphygmomanometrically and heart rate was counted from the radial pulse.

Isoprenaline infusion

In the first study isoprenaline alone was given in a dose of 8 μ g over 2 min: in the second study 80 μ g salbutamol was given over 2 min and, when the heart rate and arterial pressure had settled to around the control values some 7–8 min later, isoprenaline 8 μ g was given, as in the first study. Blood samples for PRA were taken at the same intervals following isoprenaline (Figure 1).

Tilt experiment

All subjects were familiarized with the procedure by a preliminary dummy-run. After a 45 min period of recumbency, the subject was tilted to 85° head-up on an electrically operated tilt bed (model 83000, Nesbit Evans, Wednesbury, Staffs, U.K.) at a constant rate over 90 seconds. Two tilts were performed on each subject at least 10 days apart. The first tilt was performed without the drug, whilst for the second tilt 4 mg salbutamol was given orally 1 h beforehand. Blood samples were taken just prior to tilt and after 15 and 30 min in the 85° position.

Mean arterial pressure was calculated as the diastolic pressure plus $\frac{1}{3}$ pulse pressure. Results are

Figure 1 The effect (mean $\pm$ s.e. mean) of isoprenaline 8 μ g on plasma renin before (●) and after (□) salbutamol 80 μ g. Note the attenuation and delay in the response following salbutamol. The values of PRA observed at 3, 6, 9 and 12 min are all significantly lower in the salbutamol study (t varies from 2.77 to 10.01, $P < 0.05$ to < 0.001).

expressed as mean $\pm$ s.e. mean and have been analysed using Student's t -test for paired data.

Results

Infusion study

When isoprenaline was given alone, PRA rose to a mean peak value of $72\% \pm 10$ above the mean control value by 9 min. When salbutamol was administered beforehand, the rise of PRA following the same dose of isoprenaline was both attenuated and delayed, reaching a mean peak value only $34\% \pm 8$ above the mean control value by 12 minutes. When the absolute values for PRA seen at 3, 6, 9 and 12 min were compared in the studies with and without salbutamol, they all differed significantly one from the other (Figure 1).

The haemodynamic effects of isoprenaline alone and of salbutamol and isoprenaline together were similar. With isoprenaline alone the mean maximum fall of MAP was 7 ± 1 mmHg, and the corresponding fall with both drugs was 11 ± 3 mmHg. With isoprenaline alone, the mean peak heart rate increase

was 25 ± 3 beats min^{-1} and that with both drugs was 24 ± 2 beats min^{-1} .

Tilt experiment

The resting PRA values were comparable in the control study and following oral salbutamol (1.74 ± 0.1 pmol $\text{h}^{-1} \text{ml}^{-1}$ and 1.71 ± 0.08 pmol $\text{h}^{-1} \text{ml}^{-1}$ respectively). In the control tilt, mean PRA rose to 3.35 ± 0.14 pmol $\text{h}^{-1} \text{ml}^{-1}$ and 3.5 ± 0.11 pmol $\text{h}^{-1} \text{ml}^{-1}$ at 15 and 30 min respectively. In contrast, after oral salbutamol, PRA rose to only 2.26 ± 0.1 pmol $\text{h}^{-1} \text{ml}^{-1}$ at 15 min and 2.56 ± 0.09 pmol $\text{h}^{-1} \text{ml}^{-1}$ at 30 minutes. The values observed after salbutamol were significantly lower than those observed in the control tilt (Figure 2).

Heart rate and arterial pressure, both at rest and following tilt, were not significantly different in the studies with and without oral salbutamol.

Discussion

In intact animals and in man, cardiovascular responses are the template for the assessment of

Figure 2 The response (mean $\pm$ s.e. mean) of plasma renin to tilt with ($\square$) and without ($\bullet$) oral salbutamol. The values of PRA observed at 15 and 30 min are highly significantly lower following oral salbutamol ($t=5.25$ and 4.85 respectively; $P<0.01$ for both).

agents which act upon β -adrenoceptors. However, these cardiovascular responses are inevitably obscured to some extent by compensatory reflexes. In this study

we report a novel application of adrenergically mediated renin release in an attempt to identify antagonist activity in a drug which has predominantly β_2 -agonist actions.

The net effect of any agent with an affinity for β -adrenoceptors depends upon whether that agent possesses or does not possess agonist activity and also upon the state of activation of the β -adrenoceptor at the time of administration.

Amongst the β -adrenergic agonists, we have previously shown that salbutamol is without any effect upon renin release under basal conditions in man, whereas isoprenaline briskly promotes renin release. However, in this present study we have shown that under conditions of adrenergic activation provoked by both physiological and pharmacological means, salbutamol, administered both intravenously and orally, significantly reduces the rate of renin release. It is suggested therefore that, under these circumstances, salbutamol is acting as a partial antagonist.

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