EFFECT OF A 2 WEEK COURSE OF ORAL SALBUTAMOL ON ADRENOMEDULLARY FUNCTION IN NORMAL SUBJECTS

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- 1 The adrenal medullary response to intravenous histamine infusions (0.1 and $0.4 \mu\text{g kg}^{-1} \text{min}^{-1}$ histamine base) was studied in six normal subjects.
- 2 After a 2 week course of oral salbutamol (8 mg slow release twice daily) plasma adrenaline levels, thought to reflect adrenomedullary function, were unchanged both at rest and in response to histamine infusion.
- 3 The present study does not support our original hypothesis that salbutamol may be capable of suppressing the adrenal medulla in normal subjects.

Introduction

The aim of this study was to test whether a sympathomimetic drug is capable of suppressing normal adrenomedullary function analogous to the suppression of the adrenal cortex that occurs with corticosteroid therapy. We thought this important to elucidate since it may have therapeutic implications in the treatment of asthma and may have offered an explanation of the blunted sympathoadrenal response to exercise seen in asthmatic subjects when compared with controls (Barnes *et al.*, 1981; Warren *et al.*, 1982).

Plasma adrenaline was measured at rest and in response to histamine infusion before and after a 2 week course of oral salbutamol. Histamine by infusion was used since it has been suggested that it is preferable to other methods of stimulating the adrenal medulla (Dalton *et al.*, 1981).

Methods

Six male hospital personnel who gave informed consent were studied. The mean age was 26 years (range 21-38), mean weight 69 kg (range 55-95) and mean height 1.75 m (range 1.69-1.90). All were healthy, non-atopic, not asthmatic and non-smokers. The protocol was approved by the Hospital Ethical Committee.

Each subject was studied on two occasions a fortnight apart. Between the first and second studies they took salbutamol slow release (Ventolin Spandets, Glaxo, U.K.) 8 mg twice daily. The last dose was taken between 22.00 h and 23.00 h the night before the second assessment. All studies started at 14.00 h, the subjects having abstained from caffeine contain-

ing food and drink for the previous 4 h. Each subject ate the same lunch at the same time before each experiment.

During each assessment the subject remained seated and received a saline infusion as control followed by two histamine infusions. They were not told the infusion order although saline was given first and the higher dose of histamine was always given last.

One intravenous cannula was placed in the right forearm for infusion and another in the left forearm for blood sampling. After a 20 min period to achieve a steady state, 0.9% saline was infused at 60 ml/h by means of an infusion pump (Treonic IP3 Digital Syringe Pump, Vickers Medical). Five minutes after the start of the infusion the pulse rate was taken, venous blood sampled and blood pressure measured by sphygmomanometer. Diastolic pressure was taken as the fourth Korotkov sound. The infusion was then stopped. After a 15 min rest period the procedure was repeated with histamine instead of saline at a rate of $0.1 \mu\text{g kg}^{-1} \text{min}^{-1}$ histamine base. After a further 15 min period, the procedure was again repeated but with an infusion of $0.4 \mu\text{g kg}^{-1} \text{min}^{-1}$ histamine base.

Each subject then rested supine for 30 min at the end of which period blood was sampled and the pulse rate and blood pressure were recorded. Preliminary data had shown that plasma catecholamine levels returned to baseline 15 min after cessation of histamine infusion. A further infusion of $0.4 \mu\text{g kg}^{-1} \text{min}^{-1}$ histamine base was given, the subjects remaining supine. Five minutes after the start of the infusion, pulse rate was taken, blood sampled and blood pressure recorded. The same observer, laboratory and equipment was used for all readings.

Histamine was given as the acid phosphate dissolved

in 0.9% saline. Each 1 ml sample was placed in a chilled tube containing 20 μ l of a solution of 60 mg of reduced glutathione and 90 mg of EGTA/ml as preservative. Plasma was separated in a portable centrifuge and frozen in dry ice within 2 min of sampling. It was stored at -70°C until assayed. Plasma adrenaline was assayed by a radioenzymatic method (Peuler *et al.*, 1977) with an inter-assay coefficient of variation of 4.0%. All specimens from each subject were assayed in the same batch.

Previous unpublished data suggested that histamine infusion was a larger stimulus to adrenaline secretion with subjects seated than when supine with no greater side effects. Therefore subjects were studied whilst seated in this experiment. We included measurements of plasma adrenaline with the subjects supine to confirm this difference and to test reproducibility with a previous study (Dalton *et al.*, 1981).

Data are presented as mean $\pm$ s.e. mean and significance levels were tested by the Student's *t*-test (two tailed).

Results

Figure 1 shows the plasma levels of adrenaline before and after the 2 week course of salbutamol. The data is also included in Table 1. The course of salbutamol had no significant effect on either resting or post

Figure 1 Mean ($\pm$ s.e. mean) plasma adrenaline for the six subjects. $\square$ = first assessment. $\blacksquare$ = second assessment. A = saline infusion, B = $0.1 \mu\text{g kg}^{-1} \text{min}^{-1}$ histamine infusion, C = $0.4 \mu\text{g kg}^{-1} \text{min}^{-1}$ histamine infusion with subject seated, D = resting supine, E = $0.4 \mu\text{g kg}^{-1} \text{min}^{-1}$ histamine infusion with subject supine.

infusion plasma adrenaline values. The infusion of $0.4 \mu\text{g kg}^{-1} \text{min}^{-1}$ of histamine caused a greater rise in plasma adrenaline with the subjects seated than with supine both before and after the course of salbutamol and this difference was highly significant.

Figure 2 shows the cardiovascular effects of posture and histamine infusion and values are included in Table 1. Referring to Figure 2, the mean heart rate in groups A, B and D was significantly higher than the course of salbutamol than before it. In groups C and E, the higher mean heart rate response to histamine seen after the course of salbutamol did not reach significance.

Although both systolic and diastolic blood pressure tended to be higher following the course of salbutamol, this was not significant either at rest or following infusion.

All subjects became flushed and felt warm with the higher dose of histamine and four subjects noticed a mild throbbing headache. All symptoms resolved within a few minutes of stopping the infusion.

Discussion

Two studies have shown that following a short treadmill exercise, plasma adrenaline rises significantly in normal subjects but fails to increase in asthmatic subjects (Barnes *et al.*, 1981; Warren *et al.*, 1982). One explanation of this difference could be suppression of adrenal medullary function by previous β -adrenoceptor agonist therapy in the asthmatic group, analogous to the suppression of the adrenal cortex seen with long term corticosteroid therapy. If prolonged β -adrenoceptor agonist therapy is capable of altering β -adrenoceptor numbers and function (Galant *et al.*, 1978) we postulated it may also cause an alteration in the levels of circulating adrenaline. However, despite the large dose of β -adrenoceptor agonist (salbutamol slow release 8 mg twice daily) given for 2 weeks, the subjects in the present study showed no significant suppression of their resting plasma adrenaline levels. Furthermore, their response to intravenous histamine challenge was unaltered.

Although it has been suggested for some time that histamine is capable of increasing adrenaline secretion (Burn & Dale, 1926) the mechanism is not known. Intravenous histamine probably induces dilation of small blood vessels via H_1 and H_2 receptors (Kaliner *et al.*, 1981). This causes a drop in peripheral resistance and a fall in diastolic blood pressure which probably increases sympathetic activity through a reflex arc. This would explain why higher levels of adrenaline were seen in the present experiment while histamine was infused with the subjects seated than when supine since the effect of a more upright posture would potentiate the fall in diastolic pressure caused by vasodilation. However, work done on animals

Table 1 Mean $\pm$ s.e. mean values of heart rate, plasma adrenaline, systolic and diastolic blood pressure before and after the course of salbutamol.

	Saline	Seated $0.1 \mu\text{g kg}^{-1} \text{min}^{-1}$ histamine	$0.5 \mu\text{g kg}^{-1} \text{min}^{-1}$ histamine	Supine Resting	$0.4 \mu\text{g kg}^{-1} \text{min}^{-1}$ histamine
Heart rate (beats/min)					
Pre-salbutamol	63 ± 7	68 ± 8	88 ± 8	53 ± 6	78 ± 6
Post-salbutamol	$69 \pm 6^*$	$80 \pm 4^*$	93 ± 4	$62 \pm 5^*$	87 ± 5
Adrenaline (nmol/l)					
Pre-salbutamol	0.34 ± 0.08	0.38 ± 0.06	0.85 ± 0.21	0.22 ± 0.05	0.44 ± 0.09
Post-salbutamol	0.26 ± 0.06	0.37 ± 0.08	0.65 ± 0.12	0.19 ± 0.02	0.46 ± 0.04
Systolic (mm Hg)					
Pre-salbutamol	116 ± 6	113 ± 6	111 ± 7	116 ± 6	112 ± 6
Post-salbutamol	120 ± 3	114 ± 4	107 ± 6	117 ± 2	116 ± 3
Diastolic (mm Hg)					
Pre-salbutamol	75 ± 2	70 ± 2	63 ± 3	76 ± 2	62 ± 3
Post-salbutamol	77 ± 1	75 ± 2	66 ± 3	79 ± 4	67 ± 2

* = post-salbutamol heart rate significantly higher than corresponding pre-salbutamol heart rate, ($P < 0.05$).

Figure 2 Mean ($\pm$ s.e. mean) heart rate and blood pressure changes of the six subjects. Same key as Figure 1.

using a biological assay for catecholamines suggested that in the cat histamine acts directly on the adrenal medullary cells whereas in the dog it increases adrenaline secretion via a reflex arc (Staszewska-Barczak & Vane, 1965).

Except during infusion with histamine $0.4 \mu\text{g kg}^{-1} \text{min}^{-1}$, the heart rate at the second assessment (after 2 weeks on salbutamol) was significantly higher when compared with the first assessment. Although the last dose of salbutamol had been given 16 h before the second assessment an explanation could be a prolonged effect of the salbutamol slow release preparation used. However, preliminary data suggests that in normal subjects plasma levels of salbutamol are negligible 12 h after ingestion of 8 mg slow release (personal communication, Glaxo Research Laboratories). However, adrenaline may cause a sustained rise in the heart rate and blood pressure of normal subjects 2.5 h after cessation of infusion despite its very short half-life (Brown *et al.*, 1982). The mechanism of the prolonged action of salbutamol that we observed may be similar. The lack of a significant effect of salbutamol on the heart rate response to the higher dose of histamine could be that the effect of salbutamol was small and hence lost when compared with the effect of histamine.

Our data shows that a 2 week course of oral salbutamol 8 mg twice daily does not significantly suppress resting plasma levels of adrenaline in normal subjects. Similarly the response of the adrenal medulla to infused histamine is not suppressed.

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(Received July 15, 1982,
accepted October 11, 1982)