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Hypokalaemia and other non-bronchial effects of inhaled fenoterol and salbutamol: A placebo-controlled dose-response study in healthy volunteers

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1 The hypokalaemia-inducing effects of two widely used inhaled antiasthmatic β_2-adrenoceptor agonists, fenoterol and salbutamol, were compared in six healthy male volunteers.

2 Each drug was administered in three different doses, 400, 600 and 800 μg, which were repeated three times with 30 min intervals (total doses 1200, 1800 and 2400 μg in 1 h). The treatments were given at 1 week intervals in random order in a single-blind fashion.

3 The concentration of potassium in plasma was dose-dependently reduced by both drugs with peak effects 75–90 min after the first inhalations. The hypokalaemic effect of fenoterol was significantly greater than that of equal doses of salbutamol (average ± s.d. reductions of 1.13 ± 0.32 and 0.67 ± 0.25 mEq l^{-1}, respectively, after the highest doses, $P < 0.05$). Concomitantly, decreases were noted in the amplitude of the T-wave on the ECG.

4 The concentration of cyclic AMP in plasma was measured and used as an indicator of systemic β_2-adrenoceptor agonistic effects of the drugs. Increases in cAMP were a close mirror image of the drugs' effects on potassium in plasma.

5 Plasma renin activity, noradrenaline in plasma and heart rate were also dose-dependently increased by the treatments, whereas blood pressure remained unaltered.

6 While the clinical significance of hypokalaemia induced by inhaled β_2-adrenoceptor sympathomimetics still is a matter of debate, our results point to possible differences between therapeutically equipotent doses of fenoterol and salbutamol in their propensity to cause hypokalaemia and other acute non-bronchial effects.

Keywords hypokalaemia fenoterol salbutamol cyclic AMP asthma aerosols

Introduction

Adrenaline and synthetic β_2-adrenoceptor agonists, injected in sufficient doses, cause marked decreases in the concentration of potassium (K^+) in the extracellular fluid and in blood plasma (D'Silva, 1934; Brown, 1985; Kung, 1986; Rohr *et al.*, 1986). Inhalation from metered-dose aerosol canisters is presently the clinically most commonly used form of administration of antiasthmatic β_2-adrenoceptor agonists. A hypokalaemia-inducing effect has recently been demonstrated in connection with at least one inhaled β_2-adrenoceptor agonist drug, fenoterol (Haalboom *et al.*, 1985). Concern has been expressed that such drug-induced hypokalaemia might have adverse consequences in asthmatic patients, and that it may have contributed to the increased number of deaths from asthma observed after the start of widespread use of β-adrenoceptor agonist aerosols (Haalboom *et al.*, 1985).

We have now compared in healthy volunteers the relative hypokalaemia-inducing effects of two widely used antiasthmatic β_2-adrenoceptor agonists, fenoterol and salbutamol, administered by inhalation from metered-dose aerosol canisters. Other non-bronchial effects of the drugs were assessed concomitantly. The putative mechanism by which the drugs cause hypokalaemia was monitored by quantitatively assessing the stimulation of adenylate cyclase activity, as reflected in increased circulating levels of cyclic AMP (cAMP). Another effect mediated by β_2-adrenoceptors and monitored in this study was the capacity of the drugs to increase the release of noradrenaline (NA) from sympathetic nerves, as reflected in the concentration of NA in venous plasma. Drug effects on plasma renin activity (PRA), heart rate and blood pressure, and the amplitude of the T-wave on the ECG were also monitored.

Methods

Subjects

Six healthy males participated after informed consent. They were 22–26 years old and within 20% of their ideal weight (mean 74 kg, range 65–83 kg). One was a smoker. The health of the volunteers was ascertained by medical history and a routine physical examination. No other medications were allowed. Alcoholic beverages were prohibited for 36 h prior to each session, and smoking, caffeinated beverages and chocolate were not allowed after 22.00 h on the preceding night. Each subject was always studied at the same time of the day. The study was approved by the Ethics Committee of Turku University Hospital.

Study outline

After first voiding to empty their bladders, the subjects remained supine for the duration of the sessions. A polyethylene cannula was inserted into a vein in the cubital fossa and maintained patent with a dilute solution of heparin. The contralateral arm was used for indirect measurements of blood pressure and heart rate with an automated oscillometric device (Nippon Colin 203Y). ECG cables were connected for the recording of Standard lead II. The first blood samples and recordings were taken after a minimum of 15 min had elapsed since then completion of these preparations. Thereafter, blood sampling and the recordings were repeated at 15 or 30 min intervals (see Results). Blood pressure and heart rate were always recorded twice on each occasion.

As soon as the blood sampling and recordings for time 0 (zero) were completed, the subjects sat up and took four inhalations from appropriate metered-dose aerosol canisters. The subjects had practised the use of such drug administration devices in advance, and used a standardized inhalation technique, with the lips tightly around the mouthpiece (Newman & Clarke, 1984). After four puffs, the subjects lay down again. Thereafter, the series of four puffs was repeated twice, at 30 min intervals (i.e., three times or 12 puffs in all). The study consisted of seven sessions for each subject, with at least a week between the sessions. Treatment order was randomly assigned. The study was carried out in a single-blind manner.

Drugs

Placebo (carrier gas only) and salbutamol (Salbuvent Forte®, Leiras Pharmaceuticals, Finland) were administered from identical, unlabelled canisters. Fenoterol (Berotec®, Boehringer Ingelheim, FRG) was used as it is available on the market, but with the label concealed. Each puff delivered 200 μg of the appropriate active drug. Four puffs were administered on each occasion, using two, one or zero inhalations from the canister containing the placebo to adjust the individual doses of active drug to 400, 600 or 800 μg. In addition, an experiment with four inhalations from the placebo canister was carried out in each subject.

Biochemical determinations

Blood was sampled into chilled tubes containing K_2EDTA or lithium heparin (for K^+) as anticoagulant, immediately placed on ice, and centrifuged in a refrigerated centrifuge within 30 min of collection. A minimum of 5 ml of blood was always drawn before collecting the sample for the determination of K^+ in plasma. The samples were stored at −70° C prior to analysis. All chemical determinations were done in duplicate and with the investigator unaware of the drug treatments. K^+ and Na^+ in plasma were determined using flame photometry. The concentration of cAMP in plasma was measured with the cAMP^{125} I assay system by Amersham (UK). PRA was determined using a commercially available assay kit (Phadebas Angiotensin I RIA, Pharmacia Diagnostics, Sweden).

Endogenous catecholamines in plasma were determined using high performance liquid chromatography (h.p.l.c.) with electrochemical

detection (modified from Goldstein *et al.*, 1981). In this procedure, 1 ml samples of plasma were first extracted with Al_2O_3, with dihydroxybenzylamine as the internal standard. Aliquots (50 μl) of the acetic acid extract were injected into the h.p.l.c. apparatus, which consisted of a two-piston reciprocating pump (Model 2150, LKB, Sweden), an external pulse dampener (Model LP-21, Scientific Systems Inc., USA), a Model 7125 loop injector by Rheodyne (USA), a reversed-phase C_{18} column with 5 μm particles (4.6 × 250 mm, Altex, USA) and a coulometric detector equipped with a high-sensitivity flow cell (Environmental Sciences Associates, USA). Separation of sample components was achieved with an aqueous mobile phase containing 50 mM NaH_2PO_4 with 260 mg l^{-1} heptanesulfonic acid and 5% methanol (pH adjusted to 3.10 with H_3PO_4). An oxidation potential of 0.30 mV and a reduction potential of 0.27 mV were used in the detector, which were found to produce an optimal signal to noise ratio. The lower limit of reliable detection (signal to noise ratio ≥ 3) was 0.02 nmol l^{-1} for both NA and adrenaline, with intra-assay coefficients of variation of 1.5% at concentrations exceeding 0.5 nmol l^{-1} and 10% at 0.1 nmol l^{-1}.

Drug effects on the ECG

The ECG tracings (Standard lead II) were analyzed retrospectively using quantitative manual methods, with the investigator unaware of the treatments. T-wave amplitude and duration of the QRS complex were determined and averaged from five consecutive cycles on each recording with the aid of a 7× magnifying loupe equipped with a 0.1 mm grid.

Statistical methods

Analysis of variance (ANOVA) for repeated measurements, with three within-factors (drug, dose, and time) was computed with BMDP2V programs (BMDP Statistical Software, Inc., USA). The placebo sessions were excluded from this analysis. In addition, the active treatments were compared with placebo after construction of new composite variables over time (area under the curve, AUC) for each subject and each effect parameter. This was achieved by performing a one-way ANOVA for repeated measurements and Dunnett's test for each log-transformed AUC-variable.

Results

All treatments were well tolerated. Muscle tremor and palpitations were the only subjective effects (Table 1). Three-way ANOVA revealed significant drug and dose effects (or drug × time or dose × time interactions) for the concentrations of K^+, cAMP and NA in plasma, for PRA, and for heart rate and the T-wave amplitude on the ECG (Table 2). Blood pressure showed only time-related variation. No drug × dose or drug × dose × time interactions were revealed.

One-way ANOVA for the AUC variables gave basically similar results. Table 3 shows statistically significant differences from placebo for each of the active treatments. Blood pressure (systolic/diastolic) behaved similarly after placebo and the active drugs (average increases of 4/3 mm Hg at 60 min, slight decreases thereafter).

The concentration of K^+ in plasma was dose-dependently reduced by both drugs, with average (± s.d.) maximal reductions from baseline of 1.13 ± 0.32 and 0.67 ± 0.25 mEq l^{-1} 75–90 min after the first inhalations of the highest doses of fenoterol and salbutamol, respectively ($P < 0.05$ for this difference between mean reductions, Bonferroni's *t*-test (Figure 1). Na^+ in plasma was significantly increased (Table 3) only after the highest dose of fenoterol (maximally by 1.7 ± 1.2 mEq l^{-1} at 150 min). The concentrations of cAMP and NA in plasma and PRA were dose-dependently increased by the active treatments (Figures 2, 3 and 4), whereas plasma adrenaline levels remained unchanged (0.02–0.20 nmol l^{-1}). Heart rate was increased and T-wave amplitude was decreased by both drugs in a dose-dependent manner (Figures 5 and 6). QRS duration on the ECG was not altered during the experiments (data not shown). These effects had not entirely subsided by the end of the observation period, 3 h after the last drug inhalations (Figures 1–6).

Table 1 Number of volunteers reporting subjective drug effects

	Treatments						
Effects	*P*	*S2*	*S3*	*S4*	*F2*	*F3*	*F4*
Palpitations	0	1	2	3	3	5	5
Muscle tremor	0	1	1	2	2	2	2
None	6	4	3	3	2	1	1

Note: P = placebo aerosol; S2 = two puffs of salbutamol × 3, total dose 1200 μg in 1 h. S3 = 1800 μg, S4 = 2400 μg salbutamol. Analogously F2, F3 and F4 = 1200, 1800 and 2400 μg fenoterol.

Table 2 Analysis of variance with three within factors: effects of drug, dose and time

Variable		*factor 1 = drug*	*factor 2 = dose*	*factor 3 = time*	*Interactions* 1 × 2	1 × 3	2 × 3	1 × 2 × 3
Plasma K^+	*F*	14.46	10.05	30.72	0.15	20.86	2.02	0.49
	P	0.01	0.004	0.000	0.86	0.000	0.009	0.97
Plasma Na^+	*F*	11.42	0.69	3.81	0.69	0.60	1.00	1.49
	P	0.02	0.52	0.0004	0.52	0.82	0.47	0.09
Plasma cAMP	*F*	27.33	5.84	24.11	1.38	12.75	1.54	1.21
	P	0.003	0.02	0.000	0.30	0.000	0.08	0.25
Plasma NA	*F*	11.95	4.17	29.74	0.20	5.56	2.71	0.65
	P	0.02	0.05	0.000	0.83	0.001	0.01	0.76
PRA	*F*	6.51	1.06	7.99	0.03	3.60	1.43	0.81
	P	0.05	0.38	0.000	0.97	0.001	0.12	0.71
T-wave amplitude	*F*	1.20	4.22	24.86	0.12	3.32	1.20	0.94
	P	0.32	0.05	0.000	0.88	0.002	0.26	0.54
Heart rate	*F*	13.34	7.78	19.63	0.07	8.27	3.24	0.57
	P	0.01	0.009	0.000	0.94	0.000	0.000	0.94
BP systolic	*F*	1.78	0.89	2.62	2.71	1.89	1.28	1.47
	P	0.24	0.44	0.009	0.11	0.06	0.20	0.10
BP diastolic	*F*	0.25	2.11	3.03	0.26	1.35	1.01	1.14
	p	0.64	0.17	0.003	0.78	0.22	0.46	0.32

Table 3 Significant differences from placebo for the individual treatments. Analysis of variance and Dunnett's test for log-transformed AUC variables

Variable	*ANOVA* F	P	*Treatments and significance levels* (P <) *S2*	*S3*	*S4*	*F2*	*F3*	*F4*
Plasma K^+	10.35	0.000	NS	0.05	0.01	0.01	0.01	0.01
Plasma Na^+	2.54	0.04	NS	NS	NS	NS	NS	0.01
Plasma cAMP	44.14	0.000	0.01	0.01	0.01	0.01	0.01	0.01
Plasma NA	7.86	0.000	NS	0.01	0.01	0.01	0.01	0.01
PRA	4.47	0.002	NS	NS	NS	0.05	0.01	0.01
T-wave amplitude	8.80	0.000	0.01	0.01	0.01	0.01	0.01	0.01
Heart rate	10.71	0.000	0.05	0.01	0.01	0.01	0.01	0.01

Note: S2 = two puffs of salbutamol × 3, total dose 1200 μg in 1 h. S3 = 1800 μg, S4 = 2400 μg salbutamol. Analogously F2, F3 and F4 = 1200, 1800 and 2400 μg fenoterol. No treatment effects for systolic ($F = 1.39$, $P = 0.25$) or diastolic ($F = 1.15$, $P = 0.36$) blood pressure.

Discussion

The doses of fenoterol and salbutamol administered by us were equal on a weight-for-weight basis (molar ratio, 1.0/1.6), and have been considered therapeutically equipotent (Riedel-Dibbern & Leblanc, 1972; Tandon, 1980; Lawford *et al.*, 1981; Svedmyr, 1985). The dosage exceeded usual therapeutic recommendations, but self-administered overdosage of inhaled β_2-adrenoceptor agonists is not uncommon in asthmatic patients. Our study was thus designed to assess the relative propensity of inhaled fenoterol and salbutamol to cause hypokalaemia and other non-bronchial side effects, when the drugs are taken in moderate overdoses.

Three-way ANOVA revealed highly significant drug effects and/or drug × time interactions for the reductions in plasma K^+ and the T-wave amplitude on the ECG, and for the increases in heart rate, cAMP and NA in plasma, and PRA. This statistical analysis and the results presented in Figures 1–6 indicate a greater propensity for inhaled fenoterol to cause hypokalaemia and

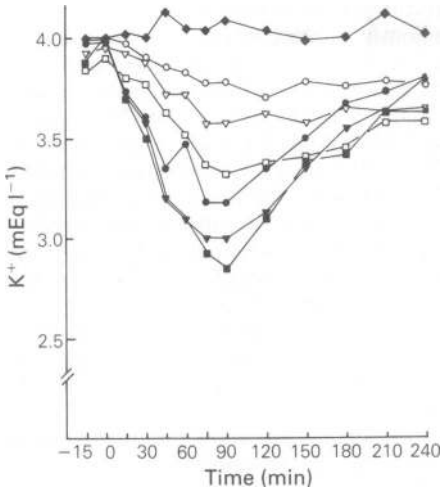

Figure 1 Effects of inhaled fenoterol and salbutamol on the concentration of potassium (K^+) in plasma. ◆, placebo aerosol; ○, salbutamol 1200 μg; ▽, salbutamol 1800 μg; □, salbutamol 2400 μg; ●, fenoterol 1200 μg; ▼, fenoterol 1800 μg; ■, fenoterol 2400 μg in 1 h.

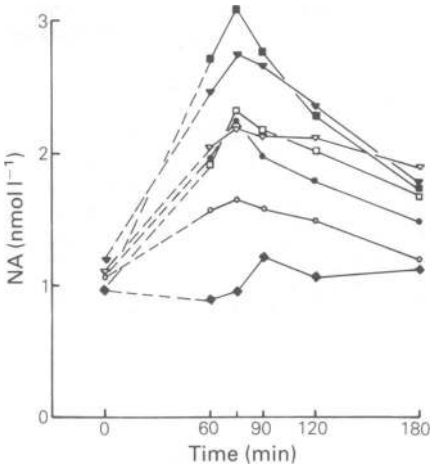

Figure 3 Effects of inhaled fenoterol and salbutamol on the concentration of noradrenaline (NA) in plasma. ◆, placebo aerosol; ○, salbutamol 1200 μg; ▽, salbutamol 1800 μg; □, salbutamol 2400 μg; ●, fenoterol 1200 μg; ▼, fenoterol 1800 μg; ■, fenoterol 2400 μg in 1 h.

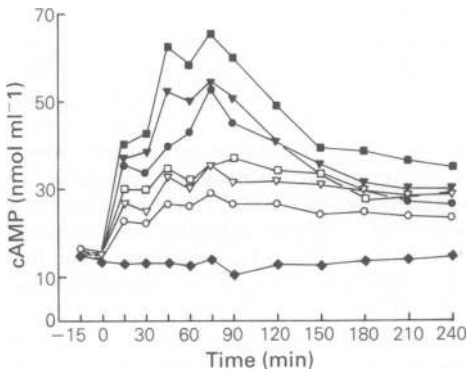

Figure 2 Effects of inhaled fenoterol and salbutamol on the concentration of cyclic adenosine monophosphate (cAMP) in plasma. ◆, placebo aerosol; ○, salbutamol 1200 μg; ▽, salbutamol 1800 μg; □, salbutamol 2400 μg; ●, fenoterol 1200 μg; ▼, fenoterol 1800 μg; ■, fenoterol 2400 μg in 1 h.

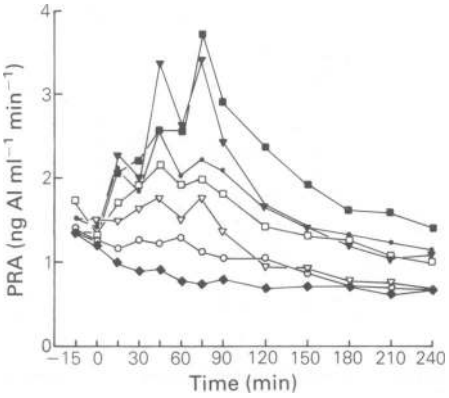

Figure 4 Effects of inhaled fenoterol and salbutamol on plasma renin activity (PRA). ◆, placebo aerosol; ○, salbutamol 1200 μg; ▽, salbutamol 1800 μg; □, salbutamol 2400 μg; ●, fenoterol 1200 μg; ▼, fenoterol 1800 μg; ■, fenoterol 2400 μg in 1 h.

other non-bronchial effects, compared with equal doses of salbutamol. Whether this reflected differences in the intrinsic pharmacological activity of the drugs or in their systemic bioavailability after administration from metered-dose aerosols, could not be determined in the present study. Insufficient pharmacokinetic studies exist to assess the relative bioavailability of the compounds (Kucharczyck & Segelman, 1985).

Long-term K^+ homeostasis is mainly controlled by the kidney; however, the liver and skeletal muscle participate significantly in the short-term regulation of extracellular K^+ levels (Brown, 1985; Vincent *et al.*, 1985). The hypokalaemia induced by adrenaline and synthetic β_2-adrenoceptor agonists is not mediated by insulin, renin or aldosterone, and it can be prevented by selective β_2-adrenoceptor blockade (Struthers *et al.*, 1983a; Struthers & Reid, 1984;

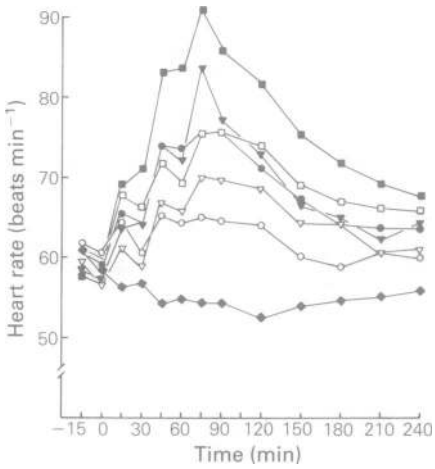

Figure 5 Effects of inhaled fenoterol and salbutamol on heart rate (HR). ◆, placebo aerosol; ○, salbutamol 1200 μg; ▽, salbutamol 1800 μg; □, salbutamol 2400 μg; ●, fenoterol 1200 μg; ▼, fenoterol 1800 μg; ■, fenoterol 2400 μg in 1 h.

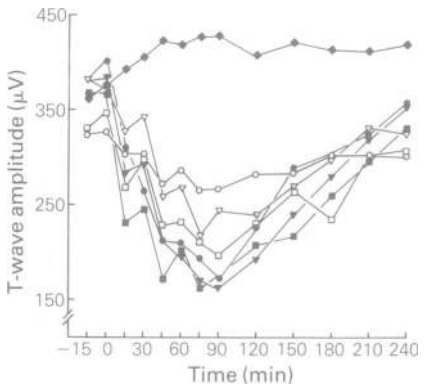

Figure 6 Effects of inhaled fenoterol and salbutamol on T-wave amplitude on the ECG (Standard lead II). ◆, placebo aerosol; ○, salbutamol 1200 μg; ▽, salbutamol 1800 μg; □, salbutamol 2400 μg; ●, fenoterol 1200 μg; ▼, fenoterol 1800 μg; ■, fenoterol 2400 μg in 1 h.

Massara *et al.*,1985). Activated β_2-adrenoceptors stimulate the Na^+–K^+ -pump via activation of the enzyme adenylate cyclase. This results in enhanced transport of K^+ from the extracellular into the intracellular compartment, and of Na^+ in the opposite direction (Brown, 1985; Vincent *et al.*, 1985; Kung, 1986). It was demonstrated in the present study that also inhaled β_2-adrenoceptor agonists, when taken in sufficient doses, are capable of inducing this acute alteration in Na^+/K^+ -homeostasis.

Intravenously administered salbutamol has previously reduced plasma K^+ in a dose- and time-dependent manner in both asthmatic subjects and healthy volunteers, with reductions averaging 0.4–0.6 mEq l^{-1} after 250 μg (Neville *et al.*, 1977; Massara *et al.*, 1985; Rohr *et al.*, 1986) and 0.9 mEq l^{-1} after 600 μg (Leitch *et al.*, 1976). An oral 4 mg dose of the drug reduced plasma K^+ in healthy subjects by 0.3 mEq l^{-1}, on the average (Salvetti *et al.*, 1978). In a previous inhalation study, plasma K^+ was slightly increased after 200 μg inhaled salbutamol (Neville *et al.*, 1977), whereas 5 mg nebulized salbutamol caused an average K^+ reduction of 0.4 mEq l^{-1} in the plasma of healthy volunteers (Smith *et al.*, 1984). In patients with hyperkalaemic periodic paralysis 800 μg inhaled salbutamol prevented completely the exercise-induced hyperkalaemia (Wang & Clausen, 1976). Systemic bioavailability of salbutamol after different routes of administration can not be directly assessed from these effects on plasma K^+, since the time course of the effect was different in these studies. Some tentative conclusions of a 10–20% bioavailability may, however, be drawn, since the hypokalaemia induced by 2400 μg inhaled salbutamol, taken in 1 h by our subjects, was slightly more pronounced than that seen after 250 μg infused intravenously in the same period of time (Massara *et al.*, 1985), but clearly smaller than that after 600 μg intravenously in 1 h (Leitch *et al.*, 1976). The hypokalaemia was more protracted in our subjects, suggesting delayed absorption, probably from the gastrointestinal tract. In any case, the systemic bioavailability of inhaled salbutamol appears to be greater than that of an oral dose, when hypokalaemia is used as the effect parameter (Salvetti *et al.*, 1978).

The reductions in plasma K^+ after inhaled fenoterol seen by us were virtually identical to those reported by Haalboom *et al.* (1985) after similar doses. We wished also to determine the time required for plasma K^+ levels to return to normal; the follow-up time of the present study, 3 h after the last dose, was not quite sufficient for complete recovery. Other inhaled β_2-adrenoceptor agonists appear to be incompletely studied with regard to effects on K^+ in plasma.

Adrenaline-induced hypokalaemia has been accompanied by corresponding ECG alterations, most notably decreases in T-wave amplitude (Struthers *et al.*, 1983a; Struthers & Reid, 1984). Similar ECG changes have been observed after intravenously infused salbutamol (Vincent *et al.*, 1985). The present study reports statistically significant, dose-related T-wave flattening also after inhaled β_2-adrenoceptor agonists. The emergence of hypokalaemia-related ECG alter-

ations points to the possible clinical relevance of the drugs' acute effects on K^+ homeostasis (Vincent *et al.*, 1985).

Adrenaline, isoprenaline and selective β_2-adrenoceptor agonists, but not noradrenaline, have increased cAMP levels in plasma; propranolol but not the β_1-antagonist metoprolol has prevented this (Endres *et al.*, 1976; Raij *et al.*, 1976; Hjemdahl *et al.*, 1983; Fairfax *et al.*, 1984). The tissue source of increased cAMP in plasma is somewhat uncertain, but the similar relationships to drug, dose and time observed for plasma K^+ and cAMP in our study suggest a close relationship between the regulatory mechanisms; the common site of these drug actions may be skeletal muscle. Previously, 800 μg inhaled fenoterol has increased cAMP in the plasma of healthy subjects by 200% (Fairfax *et al.*, 1984). In another study, 600 μg inhaled fenoterol increased plasma cAMP by 56%, whereas 300 μg inhaled salbutamol elevated cAMP in plasma by only 18% in asthmatic patients obtaining similar improvement in airway resistance after both drugs (Endres *et al.*, 1976).

Activation of presynaptic β_2-adrenoceptors on sympathetic nerve endings has enhanced stimulation-induced release of NA in various pharmacological models (Langer, 1980). Intravenously administered salbutamol and isoprenaline, but not the β_1-agonist prenalterol, have increased plasma NA levels about two-fold in humans, presumably by this mechanism (Vincent *et al.*, 1982, 1984). Propranolol abolished this effect entirely, whereas it was unaffected by β_1-adrenoceptor blockade by atenolol (Vincent *et al.*, 1982, 1984). Both inhaled β_2-adrenoceptor agonists used by us enhanced the NA levels in peripheral venous plasma quite potently: after the highest dose of fenoterol an average increase of 234% was seen. Plasma NA levels are determined by the rate of influx of NA to plasma and the plasma clearance of NA. Since β-adrenoceptor agonists have been observed to increase, and not inhibit, the clearance of NA from plasma in humans (Cryer *et al.*, 1980), it may be concluded that the increases in plasma NA concentrations observed in our study were caused by increased release of NA. Hypotension, such as that induced by nitroprusside, is a potent stimulus for NA release in humans (Grossman *et al.*, 1982), but as systolic and diastolic blood pressure were not decreased in our subjects, activation of the arterial baroreflex remains an unlikely explanation for the effects on plasma NA. It is thus suggested that the observed increases in the concentration of NA in plasma were caused by direct activation of facilitatory β_2-adrenoceptors on sympathetic nerve endings, and not by vasodilatation.

Both drugs increased PRA significantly, apparently by enhancing renin release. Release of renin from kidney juxtaglomerular cells is regulated by renal perfusion pressure, Na^+ and K^+ balance, and sympathetic nervous system activity, among other factors (Davis & Freeman, 1976; DiBona, 1982; Ganong & Barbieri, 1982). The adrenoceptor subtype mediating sympathetic neuronal stimulation is considered to be β_1, although some controversy exists in this respect (DiBona, 1982; Ganong & Barbieri, 1982). β_2-adrenoceptor agonists have, however, clearly increased PRA in several clinical studies (Salvetti *et al.*, 1978; Grospietsch *et al.*, 1980), but the mechanisms involved have not been entirely clarified. Local vascular effects may play a role: although systolic and diastolic blood pressure were not significantly altered in our subjects, changes in renal perfusion pressure cannot be excluded (DiBona, 1982). Increased sympathetic nervous activity, caused by activation of presynaptic facilitatory β_2-adrenoceptors and evidenced by increased NA levels in plasma (see above), is another plausible mechanism. Finally, the hypokalaemia induced by the β_2-adrenoceptor agonists may have been of sufficient magnitude to cause the observed increases in PRA (Davis & Freeman, 1976).

Heart rate was dose-dependently increased by both drugs, although the effect of fenoterol was clearly more pronounced than that of equal doses of salbutamol, as also previously reported in asthmatic patients (Tandon, 1980). The mechanisms for the heart rate increase may have included vasodilatation and reflex sympathetic activation of the heart, augmented NA release from cardiac sympathetic nerves, mediated by presynaptic β_2-adrenoceptors (see above), and also direct chronotropic drug effects mediated by β_2-adrenoceptors on cardiac muscle (Wikberg & Lefkowitz, 1984). Recently, the tachycardia induced by intravenous terbutaline was shown to be unaffected by β_1-adrenoceptor blockade with atenolol (Strauss *et al.*, 1986). The involvement of direct drug effects on β_1-adrenoceptors is thus unlikely.

The clinical relevance of hypokalaemia induced by β_2-adrenoceptor agonists remains a controversial issue (Kung, 1986). Whether the rapid change in the extracellular concentration of K^+ associated with the use of β_2-adrenoceptor agonists contributes to the well-known tendency of these drugs to cause disturbances in the cardiac rhythm, and the clinical significance of such a mechanism, are not known (Kung, 1986). In a previous study the effect of intravenously infused

adrenaline on the concentration of K^+ in plasma was more pronounced in previously hypokalaemic than in normokalaemic volunteers (Struthers *et al.*, 1983b). On the other hand, it was recently reported that the reduction in plasma K^+ induced by orally administered pirbuterol was proportional to the pre-existing K^+-level in asthmatic patients, hypokalaemic patients showing marked tolerance to the β_2-adrenoceptor agonist (Raimondi & Rodriguez-Moncalvo, 1987). It is, however, possible that hypokalaemia induced by overdosage of inhaled β_2-adrenoceptor agonists may have adverse clinical consequences in asthmatic patients with pre-existing low extracellular concentrations of K^+ due to use of diuretics for e.g. hypertension, or due to high circulating levels of endogenous catecholamines, caused e.g. by the stress related to a serious attack of asthma. Such enhanced hypokalaemia may be particularly deleterious in patients with concomitant heart disease or using drugs such as digitalis which sensitize the heart to hypokalaemia.

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