Systemic β -adrenoceptor responses to salbutamol given by metered-dose inhaler alone and with pear shaped spacer attachment: comparison of electrocardiographic, hypokalaemic and haemodynamic effects

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- 1 Seven normal subjects were given cumulative doubling doses of inhaled salbutamol either by metered-dose inhaler (MDI) alone, or in conjunction with a pear shaped spacer attachment (PSS). Dose increments were made every 20 min from 100 μ g to 2000 μ g.
- 2 Plasma potassium (K), electrocardiographic (ECG) and haemodynamic (HR, SBP and DBP) responses were measured at each dose increment.
- 3 There were falls in K (as mean and 95% CI) in response to salbutamol ($P < 0.001$): 3.70 mmol l^{-1} (3.46–3.95) to 3.20 mmol l^{-1} (2.91–3.49) MDI, 3.78 mmol l^{-1} (3.61–3.95) to 3.18 mmol l^{-1} (3.06–3.30) PSS.
- 4 Salbutamol produced marked ECG effects including T wave flattening ($P < 0.001$): 0.46 mV (0.24–0.68) to 0.22 mV (0.07–0.37) MDI, 0.50 mV (0.23–0.77) to 0.24 mV (0.07–0.41) PSS; and Q-Tc interval prolongation ($P < 0.001$): 0.382 s (0.372–0.392) to 0.409 s (0.397–0.421) MDI, 0.378 s (0.358–0.398) to 0.410 s (0.388–0.432) PSS. U waves occurred in five subjects with MDI and in four with PSS. S-T segment depression was present in two subjects with MDI and in three with PSS. These changes were not however associated with ventricular extrasystoles. There were also significant chronotropic effects ($P < 0.001$): 63 beats min^{-1} (57–70) to 79 beats min^{-1} (69–89) MDI, 58 beats min^{-1} (53–63) to 75 beats min^{-1} (69–81) PSS.
- 5 Comparison of dose-response curves for MDI alone and with PSS showed no significant differences, for any of the variables measured.
- 6 These results show that marked ECG and hypokalaemic effects occur with higher than conventional doses of salbutamol given by MDI alone, and that the addition of a PSS does not alter systemic β -adrenoceptor responses.

Keywords salbutamol spacer potassium electrocardiograph β -adrenoceptor

Introduction

Higher than conventional doses of salbutamol given by metered-dose inhaler (MDI) may produce substantial improvements in bronchodilatation in patients with asthma (Lipworth *et al.*, 1988b). However, these changes are accompanied by dose dependent systemic adverse

effects including hypokalaemia (Lipworth *et al.*, 1988a; Lipworth *et al.*, 1988b). In particular, recent reports have suggested that cardiac arrhythmias (Higgins *et al.*, 1987) and sudden death (Sears *et al.*, 1987) may be associated with the use of high doses of inhaled β -adrenoceptor

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agonists delivered by nebuliser. These systemic effects may be due to drug absorption from either the oropharynx (with subsequent swallowing) or lungs. The use of a 750 ml pear shaped spacer (PSS) attachment (Nebuhaler, Astra Pharmaceuticals, King's Langley) results in improved airways delivery with a marked reduction in oropharyngeal deposition (Newman *et al.*, 1984). Previous studies have shown that inhaled β -adrenoceptor agonists given by PSS cause greater bronchodilatation than either MDI or nebuliser (Cushley *et al.*, 1983; Morris *et al.*, 1984; Fuglsang & Pederson, 1986), whereas little attention has been given to systemic effects.

The purposes of the present study were two-fold. Firstly, we have investigated in detail the electrocardiographic sequelae of higher than conventional doses of inhaled salbutamol. Secondly, we have compared systemic β -adrenoceptor responses with MDI alone, with those with the PSS attachment.

Methods

Subjects and protocol

We studied seven normal healthy volunteers (four males), age (mean $\pm$ s.e. mean) 31 ± 2 years (range 23–40 years). All subjects had a normal screen including blood biochemistry and 12 lead electrocardiograph (ECG). On two separate days (1 week apart), subjects were given cumulative doubling doses of inhaled salbutamol by MDI alone, or in conjunction with a 750 ml PSS attachment (Nebuhaler). The PSS used here was chosen because it is known to reduce oropharyngeal deposition of metered-dose aerosol from 81% to 17% (Newman *et al.*, 1984). Dose increments were made every 20 min as follows: 100 μ g, 200 μ g, 500 μ g, 1000 μ g, 2000 μ g. Specially prepared metered-dose aerosol canisters were used delivering either 100 μ g or 500 μ g salbutamol per actuation, to arrive at the desired dose (Glaxo Group Research, Greenford). Previous instruction had been given in correct use of an MDI or PSS, using the methods described by Newman *et al.* (1980) and Gleeson & Price (1988) respectively. For the MDI, this involved deep slow inhalation from residual volume to total lung capacity, followed by 10 s breath-holding. For the PSS, this comprised 5 full breaths to total lung capacity, for each actuation of the aerosol canister.

Subjects attended the laboratory between 09.00 h and 10.00 h, and were laid supine throughout the 130 min study period. Caffeine ingestion was not permitted for 12 h prior to the

study. A cannula was inserted into the antecubital vein and kept patent with bolus injections of heparinised saline. A 30 min run-in period was used to establish a true baseline, with which to compare successive responses. Blood pressure was measured at 1 min intervals, and the mean of the eight lowest consistent readings used as a baseline. Two blood samples were taken at 15 min intervals during the run-in period for assay of plasma potassium (K), and the mean used as a baseline.

Ten minutes after each dose increment, the mean of four consistent measurements of blood pressure were taken. Blood was taken from the i.v. cannula, immediately centrifuged at 3500 rev min⁻¹ for 10 min, and the plasma was then stored at -20° C. An ECG trace was recorded on standard lead I for a period of 10 beats when the heart rate (on monitor) had settled to its lowest reading. The following parameters were measured from the mean of 5 beats: R-R intervals (s), Q-T interval (s), T wave amplitude (mV), U wave amplitude (mV) and S-T segment depression (mV). The Q-T interval was measured using the method described by Shamroth (1982), to account for the presence of U waves. The Bazett (1920) formula was used to correct the Q-T interval for heart rate (Q-Tc). Heart rate (HR) was calculated from R-R interval. After each dose-response study, 72 mmol effervescent K was given over the next 24 h to compensate for low extracellular levels of K.

Measurements

Systolic and diastolic blood pressure (SBP and DBP) were recorded with a semi-automated sphygmomanometer (Dinamap vital signs monitor, Critikon, USA). The ECG was recorded on a Hewlett Packard monitor and printer (set at 50 mm s⁻¹ paper speed and 0.5 mV cm⁻¹ gain). All biochemical analyses were performed in batches at the end of the study, and assayed in duplicate. Plasma K was measured by flame photometry with an IL943 analyser. The within and between values for analytical imprecision (expressed as CV) were 0.7% and 1.8% respectively, with a normal reference range for our laboratory of 3.5–5.0 mmol l⁻¹.

Statistical analysis

Repeated measures analysis of variance (MANOVA) was performed on the raw data using an 'SPSS plus' software package (Nie *et al.*, 1975). MANOVA was used to compare dose-response curves (DRC), to assess the effects of

(a) dose of salbutamol (Dose factor) (b) delivery of salbutamol by MDI alone or in conjunction with PSS (Delivery factor) (c) interaction between the mode of delivery at each dose of salbutamol (Delivery-Dose interaction). Paired Student's *t*-tests were used to compare baseline values. A probability value of less than 5% (two-tailed) was considered as being of significance for all tests.

Results

There were no differences between baseline values for MDI and PSS, for any of the variables measured. Dose-response curves (DRC) for hypokalaemic, ECG and chronotropic responses to salbutamol given by MDI alone, and in conjunction with PSS are shown in Figures 1a-d. A plateau in the DRC was not attained within our dose range for any of the measured parameters.

The results for maximum responses to salbutamol are presented as means and 95% confidence intervals. Salbutamol produced marked hypokalaemia ($P < 0.001$): 3.70 mmol l^{-1} (3.46–3.95) to 3.20 mmol l^{-1} (2.91–3.49) MDI, 3.78 mmol l^{-1} (3.61–3.95) to 3.18 mmol l^{-1} (3.06–3.30) PSS. There were no differences between the DRCs with MDI or PSS. There were highly significant falls in T wave amplitude in response to salbutamol ($P < 0.001$): 0.46 mV (0.24–0.68) to 0.22 mV (0.07–0.37) MDI, 0.50 mV (0.23–0.77) to 0.24 mV (0.07–0.41) PSS. The Q-Tc interval was also prolonged ($P < 0.001$): 0.382 s (0.372–0.392) to 0.409 s (0.397–0.421) MDI, 0.378 s (0.358–0.398) to 0.410 s (0.388–0.432) PSS. There were no differences between DRCs with either delivery system for T wave or Q-Tc responses. U waves occurred in five subjects (mean amplitude 0.09 mV) after $2000 \mu\text{g}$ salbutamol by MDI, and in four subjects (0.08 mV) by PSS. Depression of the S-T segment occurred

Figure 1 Cumulative log dose-response curves for the effects of inhaled salbutamol given by MDI alone (●) or in conjunction with PSS attachment (■), for a) plasma potassium, b) T wave amplitude, c) Q-T_c interval, d) heart rate. Values are shown as means $\pm$ s.e. mean.

Figure 2 Examples in three subjects of single lead (I) electrocardiographs (50 mm s^{-1} , 0.5 mV cm^{-1}) before and after $2000 \mu\text{g}$ inhaled salbutamol given by pear shaped spacer. Salbutamol produced T wave flattening (subjects 1, 2 and 3), U waves (subjects 1, 2 and 3) and S-T segment depression (subject 2). These changes were identical to those found with metered-dose inhaler alone.

Table 1 Blood pressure responses to inhaled salbutamol

		Salbutamol					
		Baseline	100 μg	200 μg	500 μg	1000 μg	2000 μg
SBP (mm Hg)	MDI	109 $\pm$ 3	106 $\pm$ 3	109 $\pm$ 2	107 $\pm$ 3	108 $\pm$ 3	114 $\pm$ 4
	PSS	113 $\pm$ 3	113 $\pm$ 3	111 $\pm$ 3	113 $\pm$ 3	113 $\pm$ 3	116 $\pm$ 3
DBP (mm Hg)	MDI	59 $\pm$ 2	56 $\pm$ 2	57 $\pm$ 2	55 $\pm$ 2	53 $\pm$ 1	53 $\pm$ 2
	PSS	61 $\pm$ 3	60 $\pm$ 3	59 $\pm$ 2	57 $\pm$ 2	57 $\pm$ 2	54 $\pm$ 2

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) in response to cumulative doses of inhaled salbutamol (100–2000 μg), given by metered-dose inhaler (MDI) alone or with pear shaped spacer (PSS), in seven normal subjects. Values shown are means $\pm$ s.e. mean.

in two subjects with MDI and in three with PSS (mean amplitude 0.05 mV). These ECG changes were not however associated with ventricular extrasystoles. Examples of T and U wave changes in single lead ECGs with salbutamol are shown in Figure 2.

There were also dose dependent chronotropic responses ($P < 0.001$): 63 beats min^{-1} (57–70) to 79 beats min^{-1} (69–89) MDI, 58 beats min^{-1} (53–63) to 75 beats min^{-1} (69–81) PSS, but no differences between the DRCs for MDI or PSS. Changes in blood pressure are shown in Table 1.

There was a small but significant fall in DBP ($P < 0.001$), and a small increase in SBP, after 2000 μg ($P < 0.001$).

Discussion

The results of the present study show that systemic adverse effects of higher than conventional doses of inhaled salbutamol given by MDI are not attenuated by the use of a PSS attachment. We found that doses lower than those used for

nebuliser therapy (2.5–5.0 mg) produced marked hypokalaemic and ECG effects in normal subjects. The ECG effects of salbutamol were consistent with changes due to either hypokalaemia or hypomagnesaemia (Weaver & Burchel, 1960; Eisenberg, 1986). High dose inhaled salbutamol may produce small falls in plasma magnesium (Lipworth *et al.*, 1988a) although levels were not measured here. The arrhythmogenic potential of hypokalaemia is well documented and may predispose to ventricular arrhythmias in patients with ischaemic heart disease (Stewart *et al.*, 1985; Nordrehaug *et al.*, 1985). The hypokalaemic response to salbutamol could be augmented and become clinically relevant in patients with airflow obstruction, who may be taking theophyllines (Whyte *et al.*, 1988) and corticosteroids, or by diuretics (Struthers *et al.*, 1983) for cor pulmonale or coexisting hypertension. The changes in blood pressure although significant were small, and not of clinical relevance. The magnitude of changes in SBP and DBP were similar to previously reported values for natural variability (Lipworth & McDevitt, 1989). In contrast, the hypokalaemic and chronotropic responses were considerably greater than the values required to exclude natural variation.

Only one previous study has compared objective systemic β -adrenoceptor responses with MDI and PSS (Lindgren & Larsson, 1982). This showed no difference in DRCs for tremor and heart rate responses in asthmatic patients. Interestingly there were also no differences in airways effects, although there was considerable inter-individual variability in responses.

Systemic absorption of inhaled salbutamol may occur following deposition in the lungs and oropharynx, and also from the gut after swallowing. Direct systemic absorption from the buccal mucosa should avoid first-pass metabolism by sulphate conjugation (Walker *et al.*, 1972; Morgan *et al.*, 1986; Goldstein *et al.*, 1987).

Kung *et al.* (1987) showed that mouth washing has no effect on systemic β -adrenoceptor responses to salbutamol 1 mg given by MDI. Furthermore, Collier *et al.* (1980) found that tachycardia occurs when metered-dose salbutamol aerosol is given by the inhaled route, but not by mouth spraying. These data show that absorption from the buccal mucosa is minimal, which in turn is reflected in the polarity and poor lipid solubility of salbutamol (Ohashi & Turner, 1980).

This leaves the lungs and gut as the possible remaining sites for systemic absorption of inhaled salbutamol. Radiotracer studies (Newman *et al.*, 1984) have shown that 81% of metered-dose inhaled aerosol is deposited in the oropharynx, with only 9% reaching the lungs. The addition of a PSS greatly reduces deposition in the oropharynx (17%) and improves delivery to the lungs (21%), with 56% being retained in the spacer itself. For a 2000 μ g dose of inhaled salbutamol, the addition of a PSS attachment would therefore be associated with a reduction in oropharyngeal deposition of 1280 μ g, whereas lung deposition is only increased by 240 μ g. The results of the present study showed that systemic effects of inhaled salbutamol were unaltered by the addition of PSS to MDI alone. Allowing for extensive pre-systemic metabolism of the swallowed fraction, these data would suggest that systemic effects of inhaled salbutamol are due to lung rather than gut absorption. Alternatively, improved lung delivery with PSS may have compensated for reduced oropharyngeal deposition, and gut absorption.

In summary, these results show that there are marked electrocardiographic and hypokalaemic effects with higher than conventional doses of inhaled salbutamol given by MDI. The use of a pear shaped spacer attachment did not alter systemic β -adrenoceptor responses in comparison with MDI alone.

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