Pharmacokinetics and systemic β_2-adrenoceptor-mediated responses to inhaled salbutamol

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Aims To examine whether systemic β_2-adrenoceptor responses, such as tachycardia, tremor and hypokalaemia, can be used as a surrogate for the 20 min pharmacokinetic profile of inhaled salbutamol.

Methods A retrospective analysis of eight separate published studies in healthy volunteers was performed, each with an identical protocol evaluating the early lung absorption profile of a nominal 1200 μg dose of salbutamol given by different inhaler devices. Peak postural finger tremor, plasma potassium and heart rate were assesssed.

Results We found the maximum (C_{max}) and average (C_{av}) plasma concentrations of salbutamol to be correlated ($P<0.0001$) to change in plasma potassium (C_{max} $r=0.904$; C_{av} $r=0.899$) and tremor (C_{max} $r=0.875$; C_{av} $r=0.857$). No significant correlations existed between change in heart rate and C_{max} ($r=0.425$) or C_{av} ($r=0.415$).

Conclusions Systemic β_2-adrenoceptor responses, in particular hypokalaemia and tremor, but not heart rate, appear to be good surrogates for evaluating the lung delivery of inhaled salbutamol. Consequently it is suggested that potassium or tremor responses may be used to evaluate the relative lung delivery of salbutamol from different inhaler devices.

Keywords: β_2-adrenoceptor, pharmacokinetics, salbutamol

Introduction

The relative lung delivery of inhaled salbutamol from different devices may be reliably quantified by comparing the lung bioavailability of salbutamol from the early lung absorption profile [1]. It is known that inhaled salbutamol exerts dose-related systemic effects such as tachycardia, hypokalaemia and tremor [2]. The question arises whether systemic β_2-adrenoceptor responses can be used as a surrogate for inhaled pharmacokinetics. In this respect we have performed eight separate studies evaluating the early lung absorption profile of salbutamol given by different inhaler devices [3–10]. Each study has used identical methodology in healthy volunteers and measured the 20 min pharmacokinetic profile for the same nominal 1200 μg dose of salbutamol, as well as assessing postural finger tremor, plasma potassium and heart rate.

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Methods

Subjects

Eighty-two patients were included in the studies, and their demographic data are shown in Table 1. All gave written, informed consent, and were randomized into single (investigator) or double-blind crossover studies, which were approved by the Tayside Committee for Medical Research Ethics.

Protocols

The study visits were separated by at least 3 days. At each visit patients inhaled the same nominal 1200 μg dose of salbutamol from the appropriate device. For pressurized

Table 1 Demographic data for patients in the eight studies.

Reference	*Devices studied*	n	*Mean (s.d.) age (years)*	*Mean (s.d.) % predicted FEV_1*
3	Three CFCpMDI formulations	10	20.5 (0.9)	112 (8.9)
4	CFCpMDI + Volumatic – three methods	10	20.5 (0.9)	112 (8.9)
5	Turbohaler/HFApMDI + NebuChamber	10	21 (2.2)	105 (9.5)
6	Diskhaler/Accuhaler/Easibreathe	10	24 (5.4)	103.2 (7.9)
7	CFCpMDI/HFApMDI/Diskhaler	12	20.6 (0.6)	111.4 (7.9)
8	Sidestream nebuliser/HFApMDI + Volumatic/NebuChamber	12	22 (1.4)	102 (7.4)
9	HFApMDI ± AeroChamber/Nebuhaler/Volumatic	10	22 (0.7)	103.8 (6.6)
10	Turbohaler/Accuhaler	8	21 (2.5)	106.4 (11.7)
	Pooled studies	82	21.5 (2.2)	107.0 (8.2)

CFC = chlorofluorocarbon, HFA = hydrofluoroalkane, pMDI = pressurized metered dose inhaler.

metered dose inhalers, Turbohaler and Easibreathe this was given as 12 sequential 100 μg inhalations. For the Diskhaler and Accuhaler six 200 μg inhalations were taken. For the Sidestream nebuliser the salbutamol was given as a single 1200 μg dose. Where spacer devices were used each inhalation of 100 μg was taken separately, except in one study [4] where the objective was to test different methods of inhalation via a spacer device. Inhaler technique in each case was closely monitored and as per the manufacturer's instructions.

Measurements

At each visit heart rate, tremor and potassium were measured at baseline and 20 min post inhalation. Plasma salbutamol levels were measured at 5, 10 and 20 min post inhalation.

Heart rate was measured from the standard lead II of an electrocardiogram monitor, finger tremor with an accelerometer transducer (Entran, Ealing, UK) [11], and plasma potassium analysed by flame photometry using an IL943 analyser (Instrumentation Laboratory Ltd, Warrington, UK). Plasma salbutamol was assayed by high performance liquid chromatography with solid phase extraction and fluorescence detection [12].

Statistical analysis

The maximum (C_{max}) and average (C_{av}) plasma concentrations of salbutamol were calculated as well as peak systemic β_2-adrenoceptor responses (as change from baseline). Least squares regression analysis was used to devise correlation coefficients for C_{max} and C_{av} *vs* change in heart rate, tremor and plasma potassium using SPSS for Windows (Statistical Products and Service Solutions Inc., Chicago, IL, USA).

Results

In the eight papers, a total of 24 pharmacokinetic profiles were measured. Change in plasma potassium and tremor were highly correlated to C_{max} and C_{av} (Figure 1). No significant correlations existed between change in heart rate and C_{max} or C_{av}.

Discussion

We have demonstrated that systemic β_2-adrenoceptor responses, in particular hypokalaemia and tremor, but not heart rate, appear to be a good surrogate for evaluating the early pharmacokinetic absorption profile of inhaled salbutamol. The lack of significant correlation between plasma salbutamol and heart rate is difficult to explain, but may be due to the different mechanisms involved in this β_2-response *vs* tremor or hypokalaemia. Salbutamol-induced tachycardia is due to the direct stimulation of cardiac β_2-adrenoceptors [13] as well as indirect activation of peripheral receptors [14], inducing vasodilatation and consequent reflex vagal withdrawal. In contrast, tremor and hypokalaemia are solely due to direct stimulation of skeletal muscle β_2-adrenoceptors. Presumably this explains the greater variability in heart rate response to salbutamol because of its direct and indirect actions.

We compared the lung deposition from the devices using the early pharmacokinetic profile of salbutamol in the first 20 min post-inhalation, which represents bioavailability from the lung [1]. In this situation there is no need to administer oral charcoal to block gut absorption, as the fraction absorbed from the gastrointestinal tract contributes 0.3% to the overall bioavailability over the first 30 min post inhalation [15].

All the patients were healthy volunteers, and while we appreciate that absolute drug absorption from the lung decreases with airway calibre, the relative lung bioavailability in patients with severe asthma will still be the same [16].

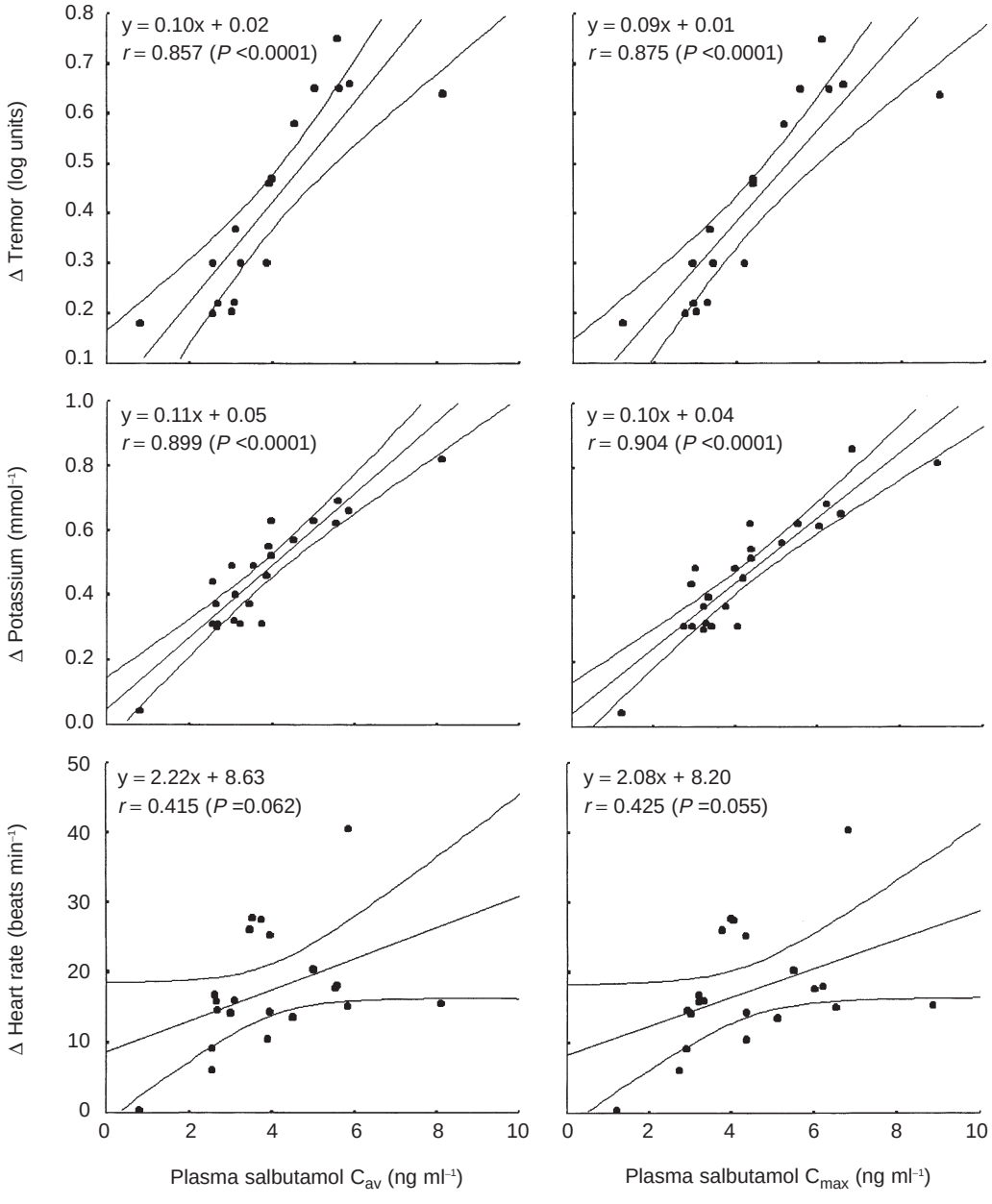

Figure 1 Mean and 95% CI from linear regression least square analysis for the average (C_{av}) and maximum (C_{max}) plasma salbutamol concentrations *vs* change from baseline in tremor ($n = 17$), plasma potassium ($n = 24$) and heart rate ($n = 21$). Each point represents a different device from a given study. Also shown are the corresponding regression equations and Pearson's regression coefficient (r).

Consequently it is suggested that potassium or tremor responses may be used to evaluate the relative lung delivery of salbutamol from different inhaler devices.

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