

Effects of airway calibre on lung delivery of nebulised salbutamol

B J Lipworth, D J Clark

Abstract

Background – A study was undertaken to test the hypothesis that airway calibre may alter lung deposition and therefore lung bioavailability of inhaled drugs as a result of narrowed airways reducing peripheral drug delivery. This was evaluated using the early lung absorption profile of salbutamol over the first 30 minutes after inhalation.

Methods – Three groups were compared: (1) 10 normal subjects with mean forced expiratory volume in one second (FEV₁) 109.5% predicted and mid forced expiratory flow (FEF₂₅₋₇₅) 103.0%, (2) 10 mild asthmatic patients with FEV₁ 102.0% and FEF₂₅₋₇₅ 82.6%, and (3) 10 severe asthmatic patients with FEV₁ 49.2% and FEF₂₅₋₇₅ 27.5% predicted. Each subject had one study visit where a single dose of nebulised salbutamol was given (40 µg/kg) via a Ventstream nebuliser with mouthpiece followed by mouth rinsing. Plasma salbutamol levels were measured at five, 10, 20, and 30 minutes after the end of nebulisation with calculation of maximal (C_{max}) and average (C_{av}) concentration over 0–30 minutes. Systemic β₂ responses (plasma potassium, tremor and heart rate) and airway responses (FEV₁, FEF₂₅₋₇₅) were measured before and 30 minutes after nebulisation.

Results – For C_{av} over 0–30 minutes the severe asthmatic patients had a lower plasma salbutamol concentration (1.31 ng/ml) than either the normal subjects (2.40 ng/ml) or those with mild asthma (2.45 ng/ml): normal subjects versus severe asthmatics 95% CI 0.30 to 1.88, mild versus severe asthmatics 95% CI 0.07 to 2.21. Airway responses as delta FEF₂₅₋₇₅ were lower in the severe asthmatic subjects (0.30 l/s) than in either the normal subjects (0.69 l/s) or those with mild asthma (0.74 l/s): normal subjects versus severe asthmatic subjects 95% CI 0.09 to 0.88, mild versus severe asthmatics 95% CI 0.04 to 0.93. Values for delta log tremor also showed attenuated responses in those with severe asthma (1.22 mg²/s) compared with normal subjects (2.00 mg²/s) or those with mild asthma (2.02 mg²/s): normal subjects versus those with severe asthma 95% CI –0.02 to 3.30, mild versus severe asthmatics 95% CI 0.02 to 3.30.

Conclusions – These results show that baseline airway calibre significantly alters the early lung absorption profile of salbutamol in patients with severe asthma. This may have implications in terms of

optimising dose and delivery of inhaled β₂ agonists in these patients.

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From first principles it may be expected that reduced small airway calibre could alter lung deposition and therefore lung bioavailability. However, there are currently few pharmacokinetic data available that specifically address this issue. Melchor *et al*¹ have shown that airway calibre does appear to affect peripheral lung deposition in a radiolabelling study in normal and asthmatic subjects in which the peripheral lung deposition was significantly higher in the normal group. The same result – that is, a 1.5-fold difference in lung deposition consequent upon an approximately twofold greater baseline forced expiratory volume in one second (FEV₁) in normal subjects – was seen with metered dose inhaler, large volume spacer, and Diskhaler delivery devices. Pavia *et al* also used radiolabelling techniques to establish that there was a direct relationship between peripheral deposition and baseline FEV₁ in asthmatic patients.²

Inhaled pharmacokinetics have been assessed using urinary excretion of sodium cromoglycate in patients with obstructive airway disease and normal controls.³ This revealed that patients with chronic bronchitis but not those with asthma had lower lung bioavailability of sodium cromoglycate than normal subjects. This in part may be explicable by the fact that the FEV₁ was lowest in the bronchitic group. A more relevant clinical issue, however, is the effect of airway calibre on the lung delivery of β₂ agonists as reduced delivery could in theory influence the bronchodilator response in acute asthma. The only data with β₂ agonists of which we are aware is retrospective. The pharmacokinetic profile of 4 mg of inhaled fenoterol from two studies using the same metered dose inhaler and protocol in normal and asthmatic subjects (FEV₁ 56% predicted) showed a twofold difference in peak plasma fenoterol concentration between the groups (1.6 ng/ml in those with asthma and 3.1 ng/ml in normal subjects).^{4,5}

In the current study we have therefore assessed prospectively the early lung absorption profile of salbutamol from a nebuliser in both mild and severe asthmatics and also in normal subjects. We have previously shown that the lung bioavailability for salbutamol may be quantified reproducibly by measuring the early lung absorption profile over the first 30 minutes

Department of
Clinical Pharmacology
and Therapeutics,
Ninewells Hospital &
Medical School,
University of Dundee,
Dundee DD1 9SY, UK
B J Lipworth
D J Clark

Correspondence to:
Dr B J Lipworth.

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Table 1 Salbutamol responses

	Normals	Mild asthma	Severe asthma
Cmax (ng/ml)	2.87* (0.26 to 2.09)	2.88 (-0.11 to 2.47)	1.69
Cav (ng/ml)	2.40* (0.30 to 1.88)	2.45* (0.07 to 2.21)	1.31
Delta log tremor (mg ² /s)	2.00 (-0.02 to 3.30)	2.02* (0.02 to 3.30)	1.22
Delta heart rate (beats/min)	10.9* (0.2 to 10.4)	12.0 (-0.1 to 12.9)	5.6
Delta potassium (mmol/l)	-0.17 (-0.19 to 0.14)	-0.22 (-0.21 to 0.07)	-0.14
Delta FEF ₂₅₋₇₅ (l/s)	0.69* (0.09 to 0.88)	0.74* (0.04 to 0.93)	0.30
Delta FEV ₁ (l)	0.22 (-0.18 to 0.59)	0.42 (-0.38 to 0.39)	0.42

Data are shown after administration of salbutamol for pharmacokinetic, airway and extrapulmonary β_2 adrenoceptor responses. Values are given as means for each group, as well as 95% CI for differences compared with subjects with severe asthma. * $p < 0.05$ for mild asthmatic or normal subjects vs severe asthmatic subjects.

after inhalation⁶ producing a sensitive index of lung deposition.⁷⁻⁹ Indeed, the oral bio-availability of salbutamol amounts to less than 0.3% for the first 30 minutes after inhalation.¹⁰

Methods

SUBJECTS

Three groups were studied: (1) 10 normal subjects of mean (SD) age 20.6 (1.0) years, FEV₁ 109.5 (8.2)% predicted, mid forced expiratory flow (FEF₂₅₋₇₅) 103.0 (14.9)% predicted, (2) 10 patients with mild asthma aged 31.7 (8.7) years, FEV₁ 102.0 (8.0)% predicted, FEF₂₅₋₇₅ 82.6 (17.6)% predicted, and (3) 10

patients with severe asthma aged 52.9 (15.2) years with FEV₁ 49.2 (15.9)% predicted, FEF₂₅₋₇₅ 27.5 (11.2)% predicted. All subjects gave written informed consent, the study having been approved by the Tayside medical ethics committee.

PROTOCOL

The subjects each had one study visit. A single dose of nebulised salbutamol (Ventolin, Allen and Hanburys, Uxbridge, UK) was given with the dose being adjusted for body weight (40 μ g/kg) via a Ventstream nebuliser with mouthpiece (Medic-Aid, Pagham, UK) driven by com-

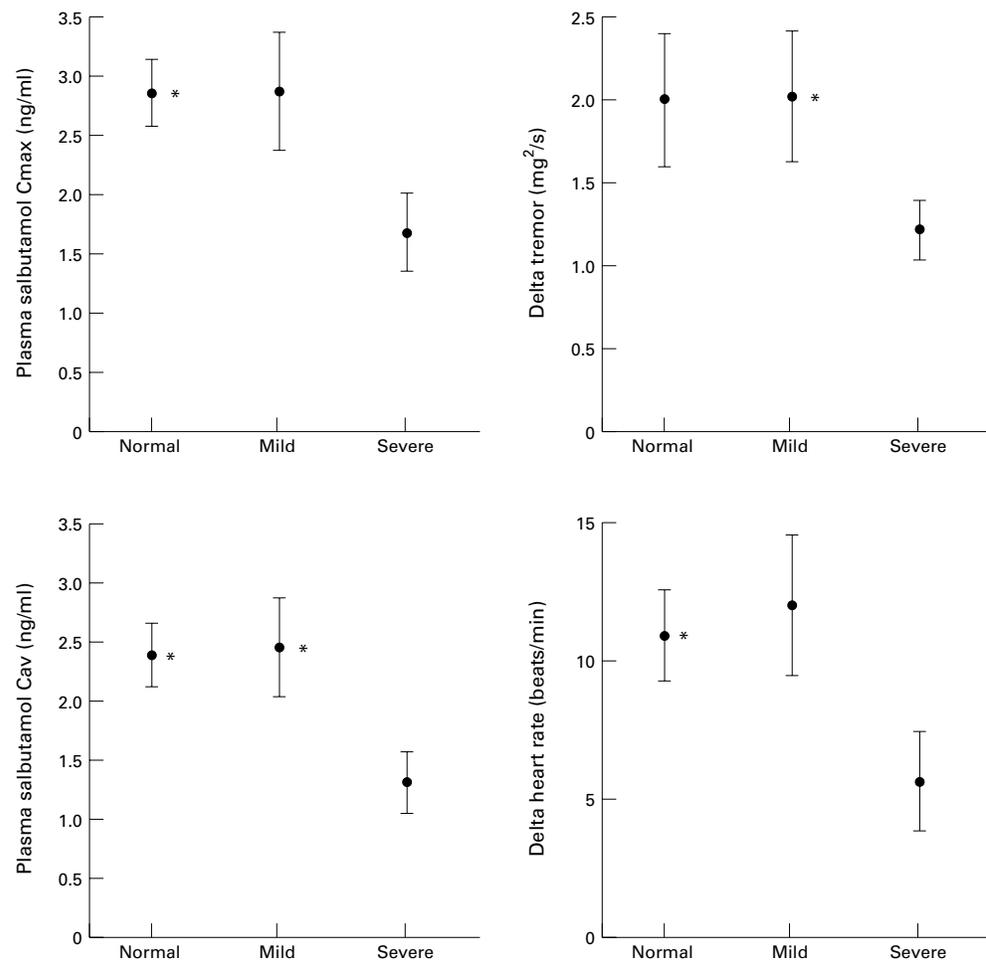


Figure 1 Mean (SE) values for plasma salbutamol peak (Cmax) and average (Cav) levels and for the increase in tremor and heart rate. * $p < 0.05$ difference between the severe asthmatic group and either the normal subjects or those with mild asthma.

pressed air at 8 l/min. The mean (range) salbutamol dose (mg) was not significantly different between the groups: normal subjects 3.28 (2.86–3.88), mild asthmatics 3.13 (2.24–3.60), severe asthmatics 3.11 (2.54–3.84). Each dose of salbutamol was given in a total fill volume of 4 ml made up with saline and nebulised to dryness over 8 minutes. Mouth rinsing was performed after completion of nebulisation in order to further obviate gastrointestinal absorption, even though the latter would be expected to be minimal.

Plasma salbutamol levels were measured at five, 10, 20, and 30 minutes after the end of nebulisation. Systemic β_2 responses were measured as plasma potassium levels, tremor, and heart rate taken at baseline and 30 minutes (all measurements made with the subject supine after nebulisation in the sitting position). Airway responses (FEV_1 , FEF_{25-75}) were measured at baseline and 30 minutes.

MEASUREMENTS

Finger tremor was measured with an accelerometer transducer (Entran, Ealing, UK),¹¹ heart rate was measured from standard lead II of an electrocardiogram monitor, and plasma potassium levels were assayed by flame photometry using an IL943 analyser (Instrumentation Laboratory Ltd, Warrington, UK). The intra-assay and interassay values for analytical imprecision were 0.41% and 1.04%, respectively.

Plasma salbutamol levels were assayed by high performance liquid chromatography (HPLC), the extraction process using silica adsorption with chromatography followed by reverse phase ion pair HPLC and electrochemical detection. The analytical imprecision for plasma salbutamol was 7.8% (intra-assay) and 6.7% (interassay). The HPLC detection limit for salbutamol was 0.02 ng/ml.

STATISTICAL ANALYSIS

The results were analysed using the Statgraphics statistical software package (STSC Software Publishing Group, Rockville, USA). Data for tremor were log transformed as it was not normally distributed. Salbutamol levels were calculated as maximal (C_{max}) and average (C_{av}) over 0–30 minutes. For all parameters comparisons were made by analysis of variance and Bonferroni's multiple range testing (set at 95% confidence limits) was used to establish where the differences between groups were significant. A probability value of $p < 0.05$ (two-tailed) was considered as being of significance.

Table 2 Mean (SE) baseline values for pharmacodynamic parameters

	Normals	Mild asthma	Severe asthma
FEV_1 (l)	5.02 (0.14)	3.81 (0.26)	1.42 (0.13)
FEF_{25-75} (l/s)	5.29 (0.24)	3.59 (0.27)	0.83 (0.12)
Log tremor (mg^2/s)	2.39 (0.15)	2.33 (0.12)	2.48 (0.11)
Heart rate (beats/min)	64.1 (2.9)	66.3 (2.0)	63.9 (2.7)
Potassium (mmol/l)	3.89 (0.07)	3.98 (0.06)	3.93 (0.06)

Values are shown for airways and extrapulmonary parameters at baseline prior to administration of salbutamol. For FEV_1 and FEF_{25-75} there were significant ($p < 0.05$) differences between each of the three groups.

Results

PHARMACOKINETICS

There were significant differences in C_{av} over 0–30 minutes between the patients with severe asthma and both normal subjects or those with mild asthma. For C_{max} there was a significant difference between normal subjects and those with severe asthma (table 1, fig 1). For both C_{av} and C_{max} there were no differences between normal subjects and those with mild asthma.

PHARMACODYNAMICS

Airway β_2 adrenoceptor responses

Baseline values (pre-salbutamol) for airway parameters showed significant differences between each of the three groups (table 2). Responses (as change from baseline) after administration of salbutamol showed a significantly lower improvement in FEF_{25-75} in the group with severe asthma compared with either the normal subjects or those with mild asthma (table 1, fig 2). For FEV_1 there were no differences in response between the three groups.

Extrapulmonary β_2 adrenoceptor responses

Pre-salbutamol baseline values for extrapulmonary β_2 adrenoceptor parameters were not significantly different between the three groups (table 2). After administration of salbutamol the group with severe asthma exhibited attenuated responses (as change from baseline) which were significantly different from those with mild asthma for tremor and from normal subjects for heart rate (table 1, fig 1). There were no differences between the three groups in potassium levels.

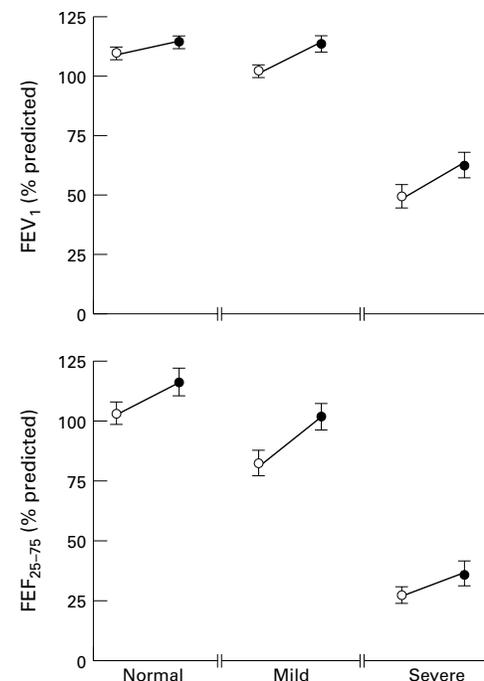


Figure 2 Mean (SE) baseline (○) and post-salbutamol (●) airway responses for FEV_1 and FEF_{25-75} as percentage predicted.

Discussion

Our results have shown differences in the early lung absorption profile of salbutamol between patients with severe asthma compared with either normal subjects or those with mild asthma. This was mirrored by attenuated β_2 adrenoceptor responses for both airway (FEF_{25-75}) and systemic (tremor) parameters. The reason for the difference in FEF_{25-75} response but not FEV_1 response may be explained by the fact that FEF_{25-75} is a more sensitive index of small airway calibre. It was interesting to note that there was no difference in the early lung salbutamol absorption profile between normal subjects and those with mild asthma in view of the difference in baseline FEF_{25-75} values. This may suggest that there is a threshold limit for FEF_{25-75} below which lung absorption begins to decline as a consequence of reduced peripheral lung delivery.

It is likely that the early pharmacokinetic profile of salbutamol represents absorption mainly from the peripheral alveolar rather than the proximal bronchial sites. Thus, in patients with severe asthma, reduced peripheral absorption of salbutamol may result in a lower systemic activity, which may translate into a more favourable therapeutic index when administering high doses to such patients. We tried to achieve optimal nebulised dose delivery using the breath assisted Ventstream which has been shown to deliver more salbutamol to the lung than a conventional jet nebuliser (Hudson Updraft II).¹² Whether or not we would have found the same differences in lung bioavailability between the groups using a more efficient device such as a spacer is worthy of further investigation.

Radiolabelling studies have shown that reduced airway calibre may have a direct effect on the peripheral deposition of inhaled drugs.¹² Zainudin *et al* in a radiolabelling study found that the bronchodilator response was determined by the total amount of drug delivered rather than its site of distribution.¹³ It is also possible that severely constricted airways may be less responsive than mildly constricted airways to the same delivered dose of β_2 agonist as a consequence of altered airways geometry.

We have shown in a previous study that the lung absorption profile for salbutamol is related to the bronchodilator response in terms of improved delivery when comparing two different nebulisers.¹² It is therefore conceivable that the severity of peripheral airway constriction may significantly influence the acute bronchodilator response to β_2 agonists as in an episode of acute severe asthma. The reduced lung bioavailability of salbutamol in severe acute asthma could be overcome by either increasing the dose or improving drug delivery. The logical extension of the present study is to evaluate plasma salbutamol pharmacokinetic data in patients with acute asthma and to correlate severity of airflow obstruction, salbutamol bioavailability, and bronchodilator responses.

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