Inhaled beta-stimulants — a study of high-dose v. conventional-dose treatment in asthmatic outpatients

P. G. BARDIN, J. R. JOUBERT

Summary

A randomised double-blind controlled trial was conducted in order to compare pulmonary function and protective effects of salbutamol 200 μg v. 1 000 μg by inhalation. Twenty-three known asthmatics took part in the study for a period of 12 weeks. Pulmonary function tests were performed at home (peak expiratory flow-rate (PEFR)) and in the laboratory (vital capacity (VC), forced expiratory volume in 1 second (FEV_1) and PEFR) before and after treatment. Bronchial responsiveness was measured as the provocative dose of histamine that caused a decrease of 30% of the area under the flow-volume curve ($AFVE_{30}$) 90 minutes after pre-treatment with the study medication. The 20 patients (10 per treatment group) who completed the study were comparable at base-line in respect of physiological and pulmonary function measurements. Median PEFR, FVC and FVC_1 did not differ between the treatment groups for the duration of study. Histamine challenge testing demonstrated a significant decrease in protection that was only seen after 8 weeks of treatment in the high-dose group ($P < 0,05$). Changes in pulse rate, blood pressure as well as side-effects were similar in the two groups. Thus treatment with higher doses of β-stimulants in outpatients had no demonstrable advantage. A significant impairment of the ability to protect against histamine-induced bronchoconstriction was shown; this may relate to β-receptor down-regulation and hence the development of tachyphylaxis.

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Conventional canisters of salbutamol (albuterol) in everyday use provide 100 μg of drug per actuation and are of proven value in the treatment of asthma.[1] The use of higher doses of the drug has been proposed,[2,3] and in clinical practice patients are frequently seen who are known to use more than the recommended 200 μg 4 times per day. These patients seldom complain of side-effects and report a good subjective response to an increase in dosage.[4]

Corris *et al.*[5] studied the dose-response to inhaled salbutamol in increasing doses in patients with chronic airflow obstruction and found a significant relationship, with the larger doses having a longer duration of action. High doses of β-stimulants have also been used to good effect in acute asthma by nebulisation and intermittent positive pressure breathing.[6] However, no studies have been done to assess the efficacy of increased doses on an outpatient population and to attempt an assessment of the response to a bronchoconstrictor, such as histamine, after use of normal and increased doses of salbutamol. The development of sub-sensitivity with long-term administration of β-stimulants has been described by Weber *et al.*,[7] but there is a paucity of data on bronchial stability after long-term use of higher doses.

An investigation was undertaken to determine if non-cumulative administration of salbutamol would produce a dose-related response in asthmatics, and confer protection against histamine challenge at the time of maximal anticipated bronchodilation.

Department of Internal Medicine, Allergy Clinic, University of Stellenbosch and Tygerberg Hospital, Parowvallei, CP
P. G. BARDIN, F.C.P. (S.A.) (Present address: Immunopharmacology Group, Medicine 1, Southampton General Hospital, Southampton, UK)
J. R. JOUBERT, M.D.

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Patients and methods

Twenty-three patients, aged 18 - 65 years, participated in the study. All had clinical asthma, a reversible decrease in forced expiratory volume in 1 second (FEV_1) of $\leq$ 70% of predicted demonstrated previously and peak expiratory flow rate (PEFR) variation $>$ 20% demonstrated for 2 weeks before the study. All patients also had at least 15% reversibility of their FEV_1 in response to a test dose of aerosolised bronchodilator (200 μg salbutamol). Patients were excluded if they were allergic to salbutamol, had had a respiratory infection within 1 month before study, had a history of angina pectoris or cardiac rhythm disturbances, diabetes mellitus, liver or kidney disease and if they were pregnant.

All patients used conventional inhaled bronchodilators. Oral β-stimulants were stopped, but oral theophylline medication and oral steroids were continued in the same doses. Excluded during the study were patients who developed a respiratory infection, those who required any change of medication and patients who were non-compliant.

All patients signed informed consent documents and the study was approved by the Ethical Committee of the Medical Faculty of the University of Stellenbosch.

Study protocol

Patients attended the allergy clinic at fortnightly intervals after all medication had been withheld for at least 6 hours. The study protocol is illustrated in Table I.

PEFR measurements

All patients were instructed in the use of a Wright peak flow meter. After instruction patients were asked to demonstrate proficiency for recording PEFR. If this was not satisfactorily shown, the manoeuvre was again demonstrated followed by patient demonstration and if necessary the procedure was again repeated until PEFR was measured accurately by all patients. At follow-up visits the patients' technique for measuring PEFR was re-assessed and improved if not correct. The patients recorded PEFR at home twice daily (morning and evening) 10 minutes after inhaling the study medication, i.e. 200 μg or 1 000 μg in a double-blind fashion.

Clinical data

A history and physical examination were peformed in all patients at every visit. Blood samples were taken for assessment

TABLE I. PROTOCOL TO INVESTIGATE TREATMENT WITH DIFFERENT DOSES OF β-STIMULANTS

Week	Outpatient activity	Research activity*
First visit (baseline I)		**Baseline histamine challenge test after no treatment for 12 hours**
1 + 2 (baseline II)	**Inhalation of β-stimulants (200 μg) and other usual medication**	**Baseline pulmonary functions and histamine challenge test after 200 μg salbutamol inhaled by both treatment groups**
	PEFRs done	**Patients randomised to treatment with salbutamol 200 μg or 1 000 μg (double-blind)†**
3 + 4	**PEFRs done, side-effects listed, study medication used every 6 hours**	**Pulmonary function tests before and after study medication Histamine challenge at 90 min**
5 + 6	**As 3 + 4**	**As for 3 + 4**
7 + 8	**As 3 + 4**	**As for 3 + 4**
9 + 10	**As 3 + 4**	**As for 3 + 4**
Last visit	**—**	**Diffusion test**

* At the end of the 2-week period, except first visit.
† Supplied by Glaxo Group Research, Greenford, Middlesex, UK.

of serum potassium (K^+) and serum theophylline levels. Patients reported side-effects at home and after use of the medication in the laboratory for a 90-minute period.

Pulmonary functions

All pulmonary function measurements were performed on an Elf pneumotac (computerised lung function system, Obstructive Pulmonary Disease Unit, Tygerberg Hospital) by the same trained pulmonary technologist. Flow-volume curves were obtained in every patient before and 60 minutes after use of the medication. The forced vital capacity (FVC), FEV_1 and PEFR were repeated until within 5% of another measurement, the highest values being used for analysis. Pulmonary function measurements were done at specific times, as shown in Table I.

Histamine challenge testing

Histamine challenge was performed at baseline I (no treatment for 12 hours) and at baseline II (90 minutes after salbutamol 200 μg in both groups). Patients then used the study medication at home (200 μg or 1 000 μg salbutamol) and visited the laboratory every 2 weeks (weeks 4 - 10) for challenge testing 90 minutes after pre-treatment with either 200 μg or 1 000 μg salbutamol.

Histamine challenge testing was done according to the method of Cockroft *et al.*,[8] utilising a DeVilbiss ultrasonic nebuliser (DeVilbiss, Somerset, Pennsylvania, USA) with graded increases in the histamine dosage of 0,03, 0,06, 0,125, 0,25, 0,5, 1,0, 2,0 and 4,0 mg/ml. Pulmonary function was measured on a Collins dry-seal spirometer coupled to a computer that measured the area under the expiratory flow-volume curve (AFVE).[9] Measurements of a decrease of 30% of the AFVE ($AFVE_{30}$) have been shown to correlate closely with a decrease of 20% in FEV_1 on antigen challenge (PD_{20}).[10] It has been used as an index of airway obstruction in various other published studies.[11–13] The challenge test was terminated when the AFVE had fallen below 30% of the initial value. A minimum period of at least 6 minutes elapsed after completion of one inhalation period and start of the next. A histamine challenge test was only performed if the initial AFVE was within 80% of previous base-line measurements.

Diffusion test

Transfer factor (T_L) was measured with a Morgan apparatus (Morgan Instruments, Chatham, Kent, UK) by means of a single breath helium-carbon monoxide dilution technique. The mean of 3 test values was used and compared with predicted normal values for every patient. The predicted normal values used for spirometry and diffusion were as proposed by Schoenberg *et al.*[14] and Cotes,[15] respectively.

Statistical methods

PEFR, FEV_1 and FVC were analysed as percentage of predicted and also as absolute values. An initial examination of the data by means of stem and leaf diagrams and distribution curves showed a non-Gaussian distribution, and hence a non-parametric test (Mann-Whitney *U*-test) was used to compare median values.

Logarithmic transformation of the histamine $AFVE_{30}$ was used for statistical calculations. The treatment groups were compared at baseline and at every 2-week period by the Mann-Whitney *U*-test. Intragroup comparisons (e.g. comparing week 10 with baseline or week 4, 6 or 8) were done by Wilcoxon's signed-rank test. All tests were two-tailed.

Results

Twenty-three asthmatic patients with mild-to-moderate airflow obstruction were studied; 20 completed the study. Three patients were withdrawn from the study because of intercurrent respiratory infections or changes in medication. Baseline data on the patients are shown in Table II. There were no significant differences between the groups with regard to pulmonary function or any of the other baseline measurements. The theophylline blood levels were therapeutic in all cases (10 - 20

TABLE II. BASELINE ANTHROPOMETRIC, PHYSIOLOGICAL AND TREATMENT DATA IN 20 MODERATELY SEVERE ASTHMATIC PATIENTS

	Treatment groups	
	200 μg (N = 10)	1 000 μg (N = 10)
Mean age ± SD (yrs)	28 ± 8,7	31 + 10,6
Sex	M = 3; F = 7	M = 1; F = 9
Mean duration of asthma ± SD (yrs)	9,0 ± 3,9	9,2 ± 3,6
Skin tests positive	8	8
IgE raised (> 200 kU/l)	4	5
FVC median % predicted (interquartile range)	87,5 (24)	87 (20,5)
FEV_1 median % predicted (interquartile range)	80,0 (24)	78,5 (22)
Median % improvement FEV_1 (interquartile range)*	15 (17)	16 (19)
$AFVE_{30}$ (median dose)† (mg/ml)	0,125	0,06
Diffusion — % predicted (mean ± SD)	101 ± 2	98 ± 4
Medication	T = 6, C = 3, O = 1	T = 8, C = 2

* After inhalation of 200 μg salbutamol.
† Median dose of histamine required at base-line testing (without preceding treatment for 12 hours) to produce reduction of AFVE > 30%.
T = oral theophylline, C = oral corticosteroids, O = oral carboxymethylcysteine.

μg/ml), except for 2 patients in the 200 μg group who had low levels at visit 1 and visit 3, respectively.

PEFR

The median values of PEFR measured during the period of study after the double-blind use at home of the different doses of bronchodilator are shown in Fig. 1. There were no significant differences between PEFRs measured by patients using conventional doses compared with those treated with higher doses of β-stimulants.

Change in FEV_1/FVC after use of medication

Median values of the changes in FEV_1 measured after use of the study medication are shown in Fig. 2. Changes in FVC were also measured (data not shown). Both medication groups showed an increase in FEV_1 and FVC after treatment but these were not significantly different in the degree of bronchodilation achieved.

Histamine challenge testing

Comparison of the two treatment groups showed no significant differences in their histamine sensitivity at baseline (Fig. 3). Significant protection against histamine was demonstrated by 200 μg salbutamol administered to both groups (baseline II) when compared with baseline histamine challenge without pre-treatment for at least 12 hours (baseline I). Both groups thus demonstrated a significant decrease in sensitivity to histamine, as could be expected after pre-treatment with β-stimulants ($P < 0,02$). No significant differences were noted in $AFVE_{30}$ between the groups at baseline II (week 2) or at weeks 4, 6 and 8. However, at week 10 a difference in histamine sensitivity had developed between the two treatment groups that almost reached statistical significance ($P < 0,06$). This was attributable to an increase in histamine sensitivity in the 1 000 μg group.

The 200 μg group had stable $AFVE_{30}$ values over the study period (Fig. 3). This was in contrast with the 1 000 μg group, which demonstrated a gradual decrease in $AFVE_{30}$ at weeks 6 and 8 and which became statistically significant at week 10 ($P < 0,05$) when compared with week 4 but not when compared with week 2. Protection against histamine was thus decreased after treatment with a higher dose for 8 weeks when compared with protection after only 2 weeks of treatment. Although it could not be demonstrated statistically, treatment after 4 weeks appeared to give more protection against histamine than was found at week 2. However, this improved protection decreased gradually to be significantly lowered at week 10 (Fig. 3).

When histamine sensitivity was assessed as change from baseline I there was less change in the 1 000 μg group (compared with the 200 μg group) at week 8. This difference just failed to reach statistical significance at week 10 ($P < 0,06$). It confirms the decrease in protection afforded by 1 000 μg of salbutamol at the 10th week.

Side-effects

Side-effects were similar in both groups, tremor being reported most frequently. Measurement of baseline and follow-up serum potassium values were normal in both groups. After treatment in the laboratory there were no differences in pulse rate and blood pressure between the two treatment groups.

Discussion

This study did not show any significant advantage for the use of higher doses of β-stimulant inhalation in patients with moderate-to-severe asthma. Assessment of symptoms, PEFR and regular pulmonary functions in the laboratory did not detect any differences between treatment with conventional doses and higher doses. A possible decrease in protection in the high-dose group against a bronchoconstrictor (histamine) was only manifest after 8 weeks of treatment.

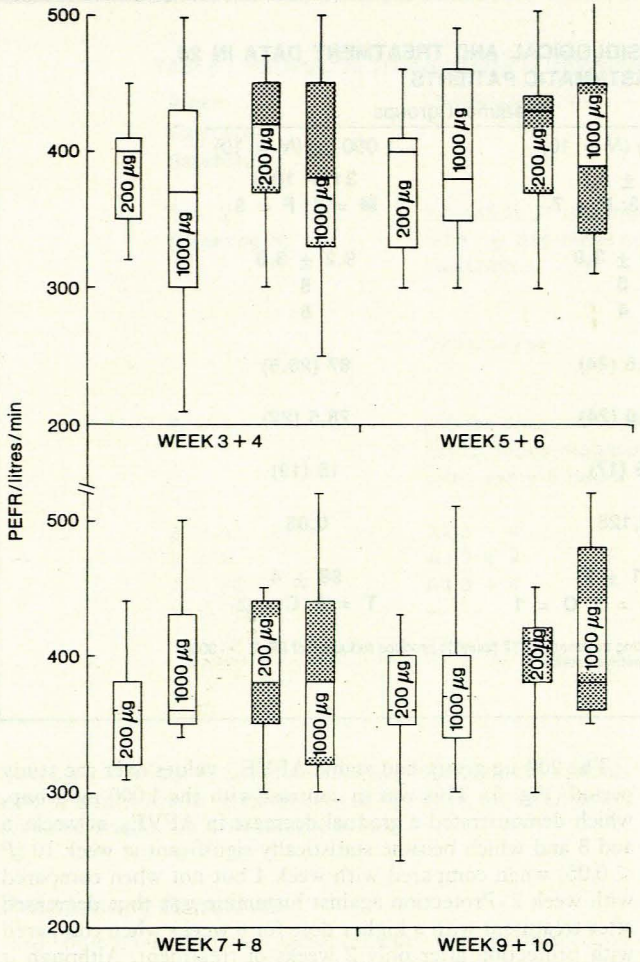

Fig. 1. Median PEFR for 16 patients measured after use of β-stimulant inhalation for 8 consecutive weeks. Absolute values are shown. Each box with bars represents the interquartile area and median of every group with maximum and minimum values. Patients used either 200 µg or 1 000 µg salbutamol — 8 patients per group. PEFRs from 4 patients were incomplete and are not included in analysis. Unshaded boxes represent morning values and shaded boxes represent evening values. No statistical differences were noted ($P > 0,05$).

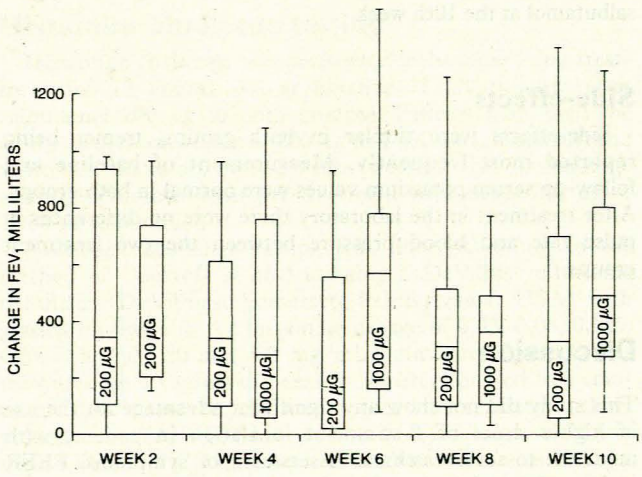

Fig. 2. Median bronchodilator response (change in FEV_1) to inhalation of either 200 µg salbutamol (10 patients) or 1 000 µg salbutamol (10 patients). Absolute values are shown. Measurements were done every 2 weeks. No significant differences were detected between the two groups.

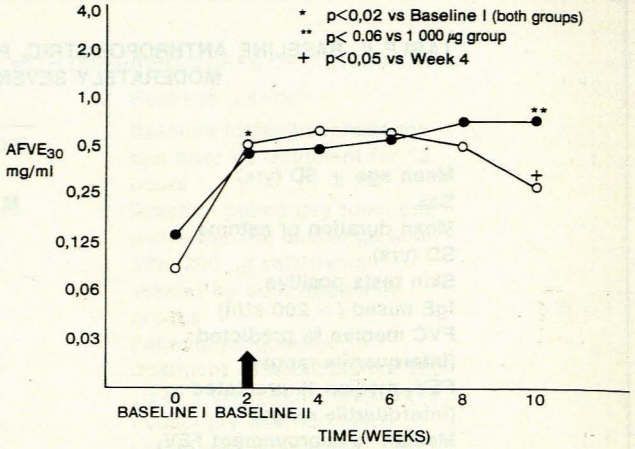

Fig. 3. Effect of 200 µg salbutamol (solid circle) and 1 000 µg salbutamol (open circle) on geometric mean histamine $AFVE_{30}$ over a period of 8 weeks. Arrow indicates start of treatment period. Baseline I represents values after no pre-treatment and baseline II values after inhalation of 200 µg salbutamol by both treatment groups.

Nelson *et al.*[16] demonstrated a linear relationship between increasing doses of albuterol (salbutamol) and increased FEV_1 by measuring the response to 1, 2, 4, 6 and 8 consecutive inhalations. With some exceptions,[17] most *in vivo* studies have shown that there is indeed a linear correlation between the log dose of bronchodilator and the response of the airways.[18–20] However, Riley *et al.*[21] showed an enhanced bronchodilator response to isoproterenol by sequential administration of the drug in divided doses. They then failed to demonstrate increasing bronchodilatation after single inhalations of this β-stimulant. Our findings could thus have been the result of the use of two inhalations of a high dose instead of multiple inhalations. From a practical point of view, the results found in the laboratory may not be achieved in an outpatient-based study when asthmatics use the current practical method of inhaling bronchodilators. Only two 'puffs' from a higher-dose bronchodilator may therefore not be better than standard treatment with the usual doses. An alternative possibility for the lack of response may be that PEFR and FEV_1 responses were on the plateau part of the dose-response curve. This is supported by the absence of a difference in side-effects between the two treatment groups. Decreased protection may consequently be more apparent on histamine challenge than in changes in FEV_1, FVC or PEFR.

This study assessed pulmonary function and bronchodilation by means of the FVC, FEV_1 and PEFR; other more sensitive measurements might conceivably have shown different results. However, Popa and Werner[22] demonstrated that measurement of the above parameters was adequate to show a significant log dose-response in 15 patients, and most other studies of this nature have not had participation of more than 20 patients.[7,16–18]

We found a significant decrease in protection against histamine-induced bronchoconstriction in the high-dose salbutamol treatment group after daily use of the medication for 8 weeks. This decrease was clearly demonstrable after 10 weeks compared with that found after 2 weeks of treatment (week 4). Relative to treatment with 200 µg, there was also decreased protection at week 10, although this difference just failed to reach statistical significance. There were no clear differences noted in the 1 000 µg group for week 2 (after 200 µg salbutamol) compared with week 10, implying that protection may have been increased at week 4 and that it had gradually decreased until week 10. A parallel decrease in PEFR, FEV_1 and FVC at 10 weeks could not be demonstrated. A similar

attenuation of the degree of protection conferred by higher doses of β-stimulants was found by Vathenen *et al.*[23] in 8 patients after only 14 days. Their study differed in design from ours, which may account for the reduction in protection observed after only 2 weeks of treatment found in that study. The major effect in their study was seen some 23 hours after the last dose. Peel and Gibson[24] failed to show decreased protection against conventional doses of salbutamol given by aerosol, a finding which is consistent with our results.

Possible causes for the decrease in protection include the development of tachyphylaxis or the intriguing possibility proposed by Tattersfield and others that treatment by β-stimulants may lead to the development of hyperreactivity in asthmatics.[23] No further data on the latter are available, although Reisman[25] demonstrated that asthma can be aggravated by adrenergic aerosol overuse. The study of tachyphylaxis in asthma is fraught with problems.[26] Certain precautions must be observed, including a suitable 'wash-out' period to remove pre-existing tachyphylaxis from previous medication. A further confounding variable may be the effect of other medication, such as theophylline and corticosteroids.[26] Our study included a modified 'wash-out' period of 2 weeks during which only β-stimulant inhalation, theophylline and steroids were used, and thereafter all medication was unchanged except for β-stimulants. The gradual development of decreased protection in the 1 000 μg group and the relative stability of the 200 μg group suggests that tachyphylaxis may have developed. It appears unlikely for other medication to explain the results, because the two treatment groups were taking almost identical medication and this was unchanged for the duration of study. If histamine provocation had been continued after the initial provocation done 90 minutes after treatment, decreased protection may have been demonstrable at an earlier stage. Conversely, it would have been interesting to see if the decrease at 10 weeks continued and became worse after further treatment with high doses of salbutamol.

The observation that higher-dose therapy with inhaled salbutamol rendered patients more vulnerable to histamine and appeared to diminish the protective effect of medication needs to be considered for its practical implications. Regular high-dose administration may not only prove to be cost-ineffective, but could possibly deprive asthmatics of the full efficacy of salbutamol prophylaxis and treatment. Our findings have to be confirmed in other outpatient-based studies to assess the clinical importance in the treatment of asthma.

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