Comparing the immediate Bronchodilatory effects of Salbutamol versus Formoterol:
A General Practice Study in Patients with Moderate Asthma

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- Asthma
- Beta-2 Stimulants
- Peak Expiratory Flow Rate (Pefr)
- Bronchodilatation
- Rescue Medication
- Salbutamol
- Formoterol

Abstract

Objectives
To determine whether there is a significant difference in the onset of bronchodilatory action between salbutamol, a short-acting beta-2 stimulant and formoterol, a long-acting beta-2 stimulant.

Background
Current guidelines for the management of moderate asthmatics include the regular use of inhaled corticosteroids in combination with long-acting beta-2 receptor stimulants. In such cases, short-acting beta-2 stimulants like salbutamol are used as rescue medication for sudden episodes of bronchoconstriction. If, however, the bron-chodilatory effect of formoterol (long-acting) is comparable to that of salbutamol five minutes after administration, the question arises whether additional short-acting bronchodilators should be prescribed for such patients.

Methods
A randomized, double blind controlled trial was conducted in a private family practice and included 20 patients with moderate asthma, randomly allocated to either the salbutamol or the formoterol group. Peak expiratory flow rate (PEFR) was measured before inhalation of the drug and repeated after exactly five minutes. The results before and after inhalation as well as the average results of each group were compared.

Results
Both formoterol and salbutamol improved the PEFR significantly, exactly five minutes after inhalation. In comparing the two drugs, there were no significant differences in PEFR improvement between the two groups.

Conclusions
The bronchodilatory action of formoterol five minutes after inhalation is comparable to that of salbutamol. Both are very effective bronchodilators, even at low therapeutic doses.

The quick onset of action of formoterol makes it unnecessary for patients using this drug to carry additional beta-2 stimulants as rescue medication. The major disadvantage of formoterol is the cost of the medication.

Introduction

Asthma is defined as a chronic inflammatory condition of the airways, which is usually allergic in origin and is characterized by hyper responsive airways, which constrict easily in response to a wide range of stimuli. This results in the characteristic symptoms of wheeze, tightness of the chest, cough and dyspnoea which are often worse in the early hours of the morning.[1] Due to the worldwide increase in the prevalence of asthma and the unacceptably high morbidity and mortality associated with the disease, management guidelines are frequently revised and updated as newer drugs become available on the market and understanding of the underlying mechanisms of the disease improves. The most recent South African guidelines for the management of chronic asthma in adults were published in May 2000.[2]

For the purpose of this study moderate asthmatics were selected, meaning that they had a peak expiratory flow rate of 60 – 80% of predicted values for their respective age, height and gender.

Current guidelines for these patients recommend the regular use of inhaled corticosteroids combined with a long-acting beta-2 stimulant, as well as the intermittent use of short-acting beta-2 stimulants as standby or rescue medication in the event of sudden or unexpected episodes of broncho-

constriction. Under ideal circumstances the need for rescue medication will be eliminated.

The aim of this study was to establish whether there is a significant difference in the onset of bronchodilatory action between salbutamol, a short-acting beta-2 stimulant and formoterol, a long-acting beta-2 stimulant.

Recent studies have shown that the onset of action of formoterol is comparable to that of salbutamol[1,3,4]. However, no studies comparing the bronchodilatory effects exactly five minutes after administration between salbutamol and formoterol have been reported. Beach et al[5] compared the speeds of action of single doses of formoterol and salbutamol with placebo in reversing metacholine-induced bronchoconstriction. All active treatments produced significantly greater bronchodilatation than placebo over the following 2-90 minute period, with no significant difference between the active treatments.

Van Noord et al[6] evaluated the profile of the bronchodilatory effect of three beta-2 stimulants, namely formoterol 24 micrograms, salmeterol 50 micrograms and salbutamol 200 micrograms in patients with stable, moderately severe asthma. They concluded that the bronchodilatory capacity of both formoterol and salmeterol was equal, similar to that of salbutamol, but that their effect lasted much longer than salbutamol – at least 12 hours in patients with asthma. However, formoterol had a more rapid onset of action than salmeterol, equal to that of salbutamol.

The question thus arises whether there is any valid reason for asthmatics using long-acting beta-2 stimulants like formoterol to carry an additional short-acting beta-2 stimulant with them to use in the event of sudden, unexpected episodes of bronchospasm.

Patients and Methods

The study design was a prospective randomised double-blind trial, conducted in a primary care setting in a private general practice in Pietersburg, capital of the Northern Province. The study period was between September 1999 and May 2000.

The study population consisted of patients suffering from moderate asthma, namely with a peak expiratory flow rate (PEFR) of 60 – 80% of the predicted values for age, height and gender. Patients were randomly allocated to either the formoterol (A) or salbutamol (B) group by means of numbers drawn from a hat. Due to the small size of the study population, male and female patients were separately randomised so that each group consisted of 5 males and 5 females. The total study population thus consisted of 20 moderate asthmatics that were randomly allocated to either the formoterol or the salbutamol group.

The identification labels on the two inhalers were removed by a third person not involved in the study and marked 'A' and 'B' respectively. Although the two canisters looked different, they were disguised with masking tape to hide their size and form, without affecting their ability to release its content. The information pertaining to the identities of the two inhalers were put in a sealed envelope until the completion of the trial. The doctor performing the trial, as well as the patients was therefore blinded to the identity of the medication. Blinding was adequately maintained throughout the study.

Criteria for inclusion were the following:

- Age 18 years or older
- Patients with clinically significant intermittent airways obstruction
- PEFR between 60-80% of predicted value for age, height and gender [7]
- Patients had to be familiar with the use of an inhaler and spacer device
- Informed, written consent had to be obtained

Patients with irreversible airways obstruction and those not familiar with the use of an inhaler were excluded from the study. The study protocol received ethical approval from the Ethics Committee of the University of Pretoria.

The study medication was administered as follows: In order to minimize the effect of poor patient coordination on the deposition of active drug in the lungs, a spacer device was used for both groups (AeroChamber® manufactured by Trudell Medical, London, Ontario, Canada). Each patient inhaled ONE puff from the spacer device. The dosage of each inhalation was the same as that which is com-mercially available, namely:

- Salbutamol (Ventolin®) 100 ug / inhalation
- Formoterol (Foradil®) 12 ug / inhalation

The PEFR of each patient was measured before inhalation of the bronchodilator. This was done to obtain a baseline value and to determine whether the patient qualified for inclusion in the study. The best of three consecutive efforts was then used as the baseline value.

The measuring instrument used to determine PEFR was a Mini-Wright® Standard Peak Flow Meter, manufactured by Clement Clarke International Ltd., Harlow, Essex, England, Model Number 3103001. PEFR measurements were repeated exactly 4 min 45 sec, 5 min and 5 min 15 sec after administration of the drug. The best of these three values represented the PEFR after inhalation. The changes in PEFR were then expressed as an absolute value (in l/min) and as a percentage change over the baseline value.

Statistics: The data were captured and analysed using software supplied by the SAS Institute Inc., namely SAS / STAT® Version 6 (4th Edition, Volumes I and II, Cary, NC, SAS Institute Inc., 1989). P-values of less than 0.05 were regarded as significant for this study. The Wilcoxon signed-ranks test was used for

comparing data within each group, while a two-way ANOVA test was used for comparing data between the groups.

Results

All twenty patients that met the criteria entered the trial and completed it successfully. They were all seen in the context of a consultation at a private general practice. None of the patients experienced any major problems using the inhaler and spacer device or the peak flow meter.

The results of the PEFR of each patient before and after the administration of the bronchodilator are tabulated in tables I and II. Table I represents the results for the formoterol group and table II the results for the salbutamol group.

In these tables the baseline PEFR value (PEFR before) is also expressed as a percentage of the expected value for age, height and gender. These percentages were calculated from tables by Gregg and Nunn[7]. The improvement in PEFR is tabulated as an absolute value (in l/min) as well as a percentage improvement over the baseline PEFR for each patient.

Table I: Group A (Formoterol Group)

Patient	Sex	Age (Yrs)	Height (cm)	PEFR Before (l/min)	% of expected value	PEFR After (l/min)	Absolute Change (l/min)	% Change
1	M	28	184	450	70%	550	+100	+ 22%
2	M	42	173	410	66%	520	+110	+ 27%
3	M	71	166	340	62%	360	+ 20	+ 6%
4	M	35	186	450	69%	620	+170	+ 38%
5	M	58	167	440	77%	500	+ 60	+ 14%
1	F	20	167	310	65%	390	+ 80	+ 26%
2	F	42	162	350	74%	390	+ 40	+ 11%
3	F	60	154	300	70%	350	+ 50	+ 17%
4	F	38	160	320	68%	420	+100	+ 31%
5	F	54	170	300	64%	360	+ 60	+ 20%
Average for Group		44,81	168,9	367	68,5%	446	+ 79	+ 21,5%
							P=0,0003	P=0,0001

Table II: Group B (Salbutamol Group)

Patient	Sex	Age (Yrs)	Height (cm)	PEFR Before (l/min)	% of expected value	PEFR After (l/min)	Absolute Change (l/min)	% Change
1	M	37	177	450	71%	540	+ 90	+ 20%
2	M	19	183	390	65%	520	+130	+ 33%
3	M	66	167	380	68%	430	+ 50	+ 13%
4	M	52	180	440	73%	490	+ 50	+ 11%
5	M	23	181	390	63%	460	+ 70	+ 11%
1	F	45	161	350	75%	390	+ 40	+11%
2	F	30	166	330	69%	400	+ 70	+ 21%
3	F	59	152	290	68%	310	+ 20	+ 7%
4	F	21	170	320	67%	380	+ 60	+ 19%
5	F	37	159	300	64%	380	+ 80	+ 27%
Average For Group		38,9	169,6	364	68,5%	430	+ 66	+ 18%
							P=0,0001	P=0,0001

The average absolute improvement in PEFR was 79 l/min for the formoterol group (table I) and 66 l/min for the salbutamol group (table II). Both these results are highly significant ($p=0.0003$ for group A and $p=0.0001$ for group B) WITHIN each group.

When expressed as a percentage, namely a 21.5% improvement in PEFR for group A and 18% for group B, the results are still highly significant ($p=0.0001$ for both groups) WITHIN each group.

Table III compares the average improvement in PEFR between the two groups, as well as average age and height.

When comparing the two groups with each other, the difference in PEFR improvement between the two groups is NOT significant ($p=0.1026$ for absolute improvement and $p=0.1136$ for percentage improvement).

The difference between the mean age of the patients in group A (44.8 years) and the patients in group B (38.9 years) is also NOT statistically significant ($p=0.06$).

The difference in mean height of the patients, namely 168.9cm for group A and 169.6cm for group B is even less significant ($p=0.540$). It is therefore important to note that the mean age and height of patients in each group had no significant impact on the results obtained in this study.

Discussion

The vast majority of asthma cases are being managed at primary care level. Every primary care physician should be familiar with the current guidelines for the management of chronic asthma in adults as well as children. In order to interpret these guidelines correctly it is necessary to evaluate the severity

Table III: Comparison of Groups

	Formoterol Group (A)	Salbutamol Group (B)	P – Value
Mean Age (Yrs)	44,8	38,9	0,06 (NS)
Mean Height	168,9	169,6	0,540 (NS)
Absolute Change In PEFR (l/min)	+79	+66	0,1026 (NS)
% Change in PEFR	+21,5%	+18%	0,1136 (NS)
NS = not significant			

of the airways obstruction by means of a peak flow meter. This device is cheap, lightweight and easy to operate. The peak flow meter enables the clinician to quantify the severity of the bronchospasm and to monitor the patient's response to treatment. Managing the asthmatic patient without a peak flow meter is like managing a hypertensive patient without a sphygmomanometer.

Visser[8] defines peak expiratory flow rate (PEFR) as the maximum flow rate attained during performance of a forced maximal expiratory manoeuvre, recorded in litres per minute and measured by a peak flow meter, of which several types are available. It is a simple, inexpensive method of objectively determining airflow limitation. Visser also mentions the shortcomings of PEFR as follows: 'The reliability of PEFR as a clinical tool for evaluation of lung mechanics is limited because of initial high flows that can occur even in obstructive disorders, before airway closing. Decreased peak flows reflect non-specific mechanical problems of the lung, patient co-operation and effort. True PEFR will increase at altitude because of the decreased air density, given that dynamic resistance is unchanged.'

The biggest limitation of this study is the small sample size, due to the fact that a single investigating doctor performed this study in the context of a solo practice and. This however does not detract from the fact that certain important observations can be made by doing research even on a limited scale in private practices.

The results of this study prove that both salbutamol and formoterol are very effective bronchodilators, with little or no difference between their onsets of action. Because current guidelines for the management of chronic asthma recommend the concomitant use of a long-acting beta-2 stimulant with inhaled corticosteroids for moderate asthmatics, the need for a short-acting beta-2 stimulant can virtually be eliminated because of the quick onset of action of formoterol. Formoterol can thus also be used as rescue medication.

The improved efficacy of newer asthma drugs, especially the long-acting beta-2 stimulants, may very well challenge the current asthma management guidelines as more study data become available.

The most important limitation for the widespread use of long-acting beta-2 stimulants is without doubt the cost of the medication. Salbutamol, especially in its generic alternative form is cheap, and the average asthmatic can afford to have a spare inhaler in the car, handbag, briefcase, gym bag etc. without applying for an increase in one's overdraft limit. Formoterol, on the other hand, must be kept in a safe place to prevent it from getting lost, because of the high replacement value of a single inhaler. The longer duration of action of formoterol may offset the impact of its higher price because a longer dosage interval is possible.

In conclusion it can be said that formoterol has been proven in previous studies to be very effective as maintenance therapy in the moderate asthmatic, but that this study additionally suggests it to be a very effective alternative to salbutamol in the event of acute bronchospasm.

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