Time course and duration of bronchodilatation with formoterol dry powder in patients with stable asthma

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Abstract

Background—Formoterol, a new β_2 agonist, is long and fast acting when given as an aerosol. The aim was to determine the onset and duration of bronchodilatation with formoterol as a dry powder compared with salbutamol dry powder and with placebo.

Methods—Fifteen patients with stable asthma with a reversibility of 15% or more participated in a double blind, within patient study. On five different days the patients received formoterol 6 μ g, 12 μ g, or 24 μ g, salbutamol 400 μ g, or placebo in random order. Forced expiratory volume in one second (FEV₁) was measured 10 minutes before, 30 minutes after, and then every hour for up to 12 hours after treatment. Specific airway resistance (sRaw) and specific airway conductance (sGaw) were measured immediately before and one, three, five, 10, 15, and 30 minutes after treatment.

Results—Formoterol 12 μ g and 24 μ g caused bronchodilatation as rapidly as salbutamol 400 μ g. Peak values were not significantly different in the active treatments. The duration of action, calculated as median time with 20% or more of the maximum achieved increase in FEV₁, was sustained for 9 hours and 16 minutes with salbutamol 400 μ g, for 9 hours and 45 minutes with formoterol 6 μ g, for 11 hours and 22 minutes with formoterol 12 μ g, and for 11 hours and 42 minutes with formoterol 24 μ g.

Conclusions—Formoterol as a dry powder at doses of 12 μ g and 24 μ g produces a rapid onset of action and has a bronchodilator effect comparable with salbutamol 400 μ g as a dry powder. The bronchodilatation was sustained for 11–12 hours. Formoterol 6 μ g caused similar bronchodilatation but more slowly and for a shorter time.

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groups then confirmed that formoterol administered as an aerosol from a metered dose inhaler causes rapid bronchodilatation and an effect lasting for at least 12 hours.^{5–8} Up to a year's treatment provides good control of asthma without inducing tachyphylaxis.^{9–12}

We investigated the efficacy of administering formoterol through a dry powder inhaler. The use of inhaled β_2 agonists in dry powder form has been increasing. Dry powder inhalers eliminate most of the coordination problems of aerosol inhalers and freon propellants are not needed, which is beneficial for the environment. We measured the bronchodilator effect, as well as the onset and duration of action, of three different doses of formoterol dry powder compared with 400 μ g salbutamol dry powder and placebo.

Methods

PATIENTS

The 15 non-smokers with stable asthma who participated had a mean age of 60 (range 39–70); seven were women. The mean forced expiratory volume in one second (FEV₁) was 61% (40%–80%) of predicted values and the mean reversibility was 23% (15%–40%). All patients took inhaled corticosteroid (median dose 650 μ g (100–1800 μ g) daily). One patient used inhaled corticosteroids plus 10 mg oral prednisolone a day. Steroid treatment was kept constant for at least one month before and during the study. Oral theophyllines were discarded 36 hours before the study treatment (two patients), oral β_2 agonists 24 hours before (two), inhaled β_2 agonists eight hours before (15), and inhaled anticholinergics eight hours before (one). None of the patients took inhaled sodium cromoglycate. The patients had no concomitant diseases, apart from two patients (cases 3 and 4) who had mild hypertension. Table 1 shows the patients' characteristics. The study was approved by the ethical committee of the University Hospital of Umeå.

STUDY DESIGN

All 15 patients received, on a double blind randomised basis, formoterol 6 μ g, 12 μ g, or 24 μ g, placebo, or salbutamol 400 μ g as a dry powder on five different days. The treatments were given every other day during the week. The drugs were given as capsules with a standard powder device (fig 1) by four deep

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Formoterol is a potent and highly selective β_2 adrenoceptor agonist^{1,2} which has been used in Japan for several years as an oral preparation.³ Surprisingly, a study by Löfdahl and Svedmyr showed that inhaled formoterol produced a much more long lasting bronchodilatation than oral formoterol.⁴ Several

Table 1 Characteristics of patients in study

Case No	Age (years)	Sex	Duration of asthma (years)	FEV ₁ (%)		
				Predicted values	Reversibility	Treatment*
1	54	F	4	69	21	None
2	59	M	17	77	18	None
3	62	M	20	60	19	Amiloride, hydrochlorothiazide
4	68	F	30	40	26	Amiloride, frusemide
5	66	F	25	64	27	None
6	70	M	23	76	15	None
7	63	M	30	67	19	Inhaled anticholinergic
8	60	M	8	46	26	None
9	53	F	10	59	18	None
10	65	F	15	67	19	None
11	54	M	28	62	24	None
12	69	F	15	51	39	None
13	64	M	40	53	40	Oral β_2 agonist, corticosteroid, theophylline
14	56	M	13	44	18	Oral β_2 agonist, theophylline
15	39	F	6	80	19	None
Mean	60		19	61	23	
Range	39–70		4–40	40–80	15–40	

*In addition to inhaled corticosteroid and β_2 agonist.

Figure 1 Dry powder device. 1 = Capsule with dry powder; 2 = buttons which when pressed together cause the needles inside to puncture the capsule; 3 = air intake; 4 = grating, through which only the powder is allowed to pass; 5 = outlet to mouth and lungs.

inhalations from the FRC. The schedule was the same on all five days. The patients arrived at the laboratory between 7 am and 9 am having not taken any inhaled bronchodilators during the previous eight hours. FEV₁ was measured after at least 30 minutes' rest. If this baseline value was within 15% of the

mean baseline value on previous study days patients received the planned drug. If not, they returned on another day.

METHODS

Airway resistance was measured by using a body plethysmograph (Master Lab Body, Erich Jaeger). The study drug was taken by the patient inside the plethysmograph. Before and one, three, five, 10, 15, and 30 minutes after treatment specific airway resistance (sRaw) and specific airway conductance (sGaw) were measured during quiet breathing and evaluated from the mean value of three to five technically correct resistance loops and two to five intrathoracic gas volume slopes. The breathing frequency was controlled at 20 breaths a minute with a metronome. The patients practised this procedure before the study. FEV₁ was measured after 30 minutes and then every hour for up to 12 hours. If the patients reported worsening symptoms after inhalation of the study, the drug salbutamol 400 μ g was given and the last measured value was carried forward to be used in analyses. A standard dry bellows spirometer (Vitalograf) was used throughout the study to measure FEV₁, the highest of at least three measurements being recorded. Patients refrained from drinking caffeinated drinks eight hours before and throughout the study days.

STATISTICAL ANALYSIS

Analysis of covariance was used to provide estimates of the contrasts of interest and to test for significance. The model used reflected the within patient structure of the design and incorporated terms to represent patient, treatment period, and baseline effects. Version 6.04 of the SAS statistical package (particularly the GLM period procedure) was used to evaluate the model and to tabulate the results. A p value <0.05 was considered to be significant, and confidence intervals were calculated from the estimate of the

Table 2 Lung function after study treatments. Values are means (SD).

	Formoterol			Salbutamol 400 µg
	6 µg	12 µg	24 µg	
FEV ₁ (l)*				
Basal	1.81 (0.48)	1.82 (0.43)	1.77 (0.42)	1.75 (0.40)
Peak	2.18 (0.50)	2.28 (0.48)	2.25 (0.46)	2.21 (0.46)
Median effect at 30 min†	77 (19.7)	89 (26.9)	75 (17.6)	87 (19.9)
Median duration‡	9 h 45 min (3 h 56 min)	11 h 22 min (3 h 42 min)	11 h 42 min (1 h 55 min)	6 h 16 min (2 h 45 min)
AUC	3.11 (0.07)	3.16 (0.07)	3.18 (0.07)	3.06 (0.07)

AUC = area under the curve.

*Including values carried forward.

†Percentage of maximum increase in FEV₁ achieved with study drug.

‡≥12 hours was recorded as 12 hours.

Figure 2 Mean specific airway conductance (sGaw) during the first 30 minutes after study treatments; * $p < 0.05$, + $p < 0.0005$ when comparing the active drugs with placebo. Figure 3 Mean FEV₁ during the 12 hours after administration of study treatments. The last values before rescue treatment have been carried forward. NS = No significant difference between formoterol 6 µg or salbutamol 400 µg compared with placebo. At all other time points differences between the active drugs and placebo were significantly different ($p < 0.05$ — $p < 0.0001$; ** $p < 0.005$, *** $p < 0.0001$). The increase in FEV₁ at 30 minutes and one and two hours after treatment did not differ significantly between the active drugs.

standard error produced by the GLM procedure. The FEV₁ areas under the curve were analysed by the trapezoidal rule.

Results

ONSET

Figure 2 shows the onset of bronchodilatation measured as improvement in sGaw. After one minute all active drugs had a significantly higher sGaw than placebo. The increase in sGaw was also calculated as the median percentage of the maximum increase in sGaw. At three and five minutes after dosing the increases were 18% and 36% for formoterol 6 µg, 48% and 50% for formoterol 12 µg, 49% and 50% for formoterol 24 µg, and 37% and 56% for salbutamol 400 µg.

The increase in sGaw for formoterol 12 µg and 24 µg and for salbutamol 400 µg was almost identical during the first 30 minutes after inhaling them. Formoterol 6 µg caused a smaller change in sGaw compared with formoterol 12 µg and 24 µg and salbutamol 400 µg. Formoterol 24 µg produced a significantly ($p < 0.05$) higher sGaw than formoterol 6 µg between three and 30 minutes after dosing.

BRONCHODILATATION CAPACITY

Figure 3 and table 2 show the mean FEV₁ values, including any values carried forward after rescue treatment. Thirty minutes after treatment all active drugs had reached 75%–89% of their maximum achieved bronchodilatation. There were no significant differences between the FEV₁ values for formoterol 6 µg, 12 µg, and 24 µg and salbutamol 400 µg 30 minutes after dosing or after one and two hours. The mean maximum individual peak FEV₁ values for formoterol 6 µg, formoterol 12 µg, and salbutamol 400 µg all occurred one hour after treatment and for formoterol 24 µg two hours after treatment.

DURATION

Compared with placebo, formoterol 12 µg and 24 µg caused a significant increase in FEV₁ for up to 12 hours and formoterol 6 µg for up to 10 hours (fig 3 and table 2). After five hours the effect of salbutamol fell and was similar to that of placebo. Between three

hours and 12 hours after treatment the two highest doses of formoterol increased FEV₁ significantly more than salbutamol 400 µg.

The duration of bronchodilatation was dose dependent. The area under the curve was significantly higher for all formoterol doses compared with salbutamol 400 µg and placebo. Formoterol 12 µg and 24 µg had a significantly larger area under the curve than formoterol 6 µg, but there was no significant difference between formoterol 12 µg and 24 µg (table 2).

The increase in FEV₁ after formoterol 24 µg was consistently higher than after formoterol 6 µg, although it reached significance only after 10 hours. The rise in FEV₁ after formoterol 24 µg did not become significant compared with formoterol 12 µg until 12 hours after dosing.

Five patients had rescue treatment on a total of 13 occasions; with placebo twice after 125 minutes, with formoterol 6 µg after 425, 605, 668, and 670 minutes, with formoterol 12 µg after 365 and 670 minutes, with formoterol 24 µg after 500 and 670 minutes, and with salbutamol 400 µg after 302, 490, and 668 minutes.

Discussion

The onset of bronchodilatation, measured as sGaw, was almost identical with formoterol 12 µg and 24 µg and salbutamol, the classic reference drug used for rescue treatment. The maximal bronchodilatation achieved was also similar for the two drugs. This is in agreement with studies using formoterol from metered dose inhalers by Derom *et al.*⁶ and Maesen *et al.*⁷

Thirty minutes after treatment all active drugs had almost reached their maximum bronchodilatation, and there was no significant difference between values 30 minutes, one hour, or two hours after treatment.

The duration of bronchodilatation for formoterol dry powder was as expected significantly longer than for the shorter acting salbutamol and placebo. Formoterol 12 µg and 24 µg had similar duration of action, whereas it was slightly shorter for formoterol 6 µg. A common way to express duration of bronchodilatation is as the length of time the FEV₁ is 15% or more above baseline values. We chose the method described by Arvidsson *et al.*¹³ and have expressed the duration as the median time with 20% or more of the maxi-

mum achieved bronchodilatation because the asthma was moderately reversible in our subjects. With this descriptive method the duration of bronchodilatation was 11–12 hours for formoterol 12 µg and 24 µg, which is similar to the results in studies on inhaled formoterol from metered dose inhalers.^{6–8}

We conclude that formoterol dry powder 12 µg and 24 µg had a rapid onset of action and a bronchodilator effect comparable with that of salbutamol 400 µg dry powder. The bronchodilatation was prolonged for up to 11–12 hours. There was a dose-response relation, with shorter duration and slower onset for formoterol 6 µg. Formoterol 12 µg seems to be the most favourable dose, but because variation in the duration of bronchodilatation is large between subjects there may be a need for more than one recommended dose for clinical practice.

This study was presented in abstract form at the annual meeting of the American Thoracic Society in Anaheim, California, in May 1991.

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BOOK NOTICES

The Mast Cell in Health and Disease. M A Kaliner and D D Metcalfe. (Pp858; \$195.00). New York: Marcel Dekker, 1993. 0 8247 8732 3

Over the past decade there have been many advances in several aspects of an understanding of the biology of the mast cell. The possibility of culturing mast cells, the discovery of several growth factors responsible for mast cells, the recognition of mast cell heterogeneity, the cloning of the IgE receptor and the identification of a wide array of mediators and, more recently, of cytokines that may be released from these mast cells have been major strides that have re-emphasised the potential for the mast cell in initiating and participating in immunological and inflammatory responses in various tissues. This volume is a comprehensive review of the biology of the mast cell in health and disease and of its potential involvement in various diseases such as asthma, urticaria, food allergy, parasitic infestations, arthritis, scleroderma, and systemic mast cell disease. Approximately half of the 32 chapters deal with the basic aspects of mast cell ultrastructure, function, development, heterogeneity and release of mediators/cytokines, while the remaining chapters focus on the potential contribution of mast cells to disease. Because the production of this book resulted from a meeting, the editors have included the discussion that ensued amongst the contributors following each presentation. This section often gives insight into the uncertainties in some areas at the forefront of mast cell research. This book is volume 62 in the Lung Biology in Health and Disease series and can certainly be considered as the definitive comprehensive state-of-the-art work to be entirely devoted to the mast cell. Although the latest references quoted are up to 1991, it will remain the authoritative reference work on the mast cell for many years to come. It should be of interest to a wide audience of researchers across many disciplines, particularly to those involved in asthma, allergy and immunology, and in pharmacology. The clinician will also find many of the chapters relating mast cells to disease of interest. At nearly £130 this book should be made available in any respectable library, although anyone with more than a passing interest in mast cell research or mast cell related disease should consider investing in a copy.—FC

Radiology of Thoracic Trauma. Paul Stark. (Pp166; £50). Oxford: Butterworth-Heinemann, 1992. 1 56372 044 3.

This slim single author book contains material condensed from an instructional course given over five years at the Radiological Society of North America meetings. The book is divided into 11 short chapters covering all the forms of thoracic trauma likely to be encountered in modern America. Given that each topic is essentially a summary of the course material, the coverage of the different entities is a little uneven. For example, the chapter on chest cage injuries is devoted almost entirely to rib fractures and their sequelae; there is no mention of imaging of the traumatised vertebral

column—a challenging area to evaluate by plain film or cross sectional imaging. The similarly difficult area of tracheobronchial fracture also deserves fuller coverage. These small deficiencies do not diminish the many good things in this book: there is an outstanding section on lung injury which includes a particularly clear and well illustrated section on lung contusion, laceration, and haematoma. An important chapter on the imaging of the potentially ruptured thoracic aorta is also a model of clarity. All aspects of thoracic trauma are generously illustrated and this reflects the author's great personal experience (readers will want to congratulate the author on his collection of such dramatic illustrative material and for staying the course in such a dangerous place). The high quality of the radiographs and computed tomograms, many of which must have been obtained in extreme circumstances, are a tribute to the radiographers who took them. Further evidence of the author's interest and authority on thoracic trauma is shown in the number of his contributions to the literature in the lists of references at the end of each chapter. The size of this "short monograph", as the author calls it, lends itself to rapid absorption and a great deal can be gained from it in a short time. As a consequence it is, quite appropriately for such a didactic book, only lightly referenced. In an ideal world every casualty department would have a copy of this book and every admitting doctor would have read it.—DMH

Signal Transduction in Lung Cells. Jerome S Brody, David M Center, Vsevolod A Tkachuk. (Pp704; \$195.00). New York: Marcel Dekker, 1993. 0 8247 8813 3.

This is the 65th in the impressive series of Lung Biology in Health and Disease. The topic chosen by Claude Lenfant for this volume is a rapidly advancing topic concerning the pathways involved in cellular responses to both external and internal messages. The authors are primarily from the USA and the former USSR, and the volume arose from international collaboration and a subsequent scientific meeting. The field of intracellular signalling has shown great advances over the last 10 years and a complex pathway of events, somewhat reminiscent of the Krebs cycle, has evolved. This is therefore a difficult field to make user friendly. The book consists of eight basic introductory chapters. Unfortunately the first is full of jargon, abbreviations and moves too rapidly from the simple scheme outlined in the first table (perhaps this reflects the multiple authorship). Thus, the first impression tends to confirm the view of the non-expert that this is a complex field that they may never wish to understand. However, the second chapter provides a better introduction and an extensive review on the regulation, structure and function of G protein linked receptors. The remaining introductory chapters are extensive reviews with historical perspectives and experimental detective work providing a background that is most relevant to scientists wishing to enter the field of signalling. The second section concerns epithelial cells where work has been less extensive. The application of the basic concepts is in its infancy, but these chapters are generally very readable with the exception of chapter 11 on growth factors which suffers from the lack of any tables or figures. The remaining sections relate to

smooth muscle cells, endothelial cells, and cells of the immune system (macrophages, lymphocytes, and mast cells). The chapters cover the role of cytokines, G proteins, protein kinases, and phosphatases in a way that may be more relevant to the clinical scientist. In summary, this is predominantly a reference book to be dipped into rather than read, except by the dedicated or training scientist in the field. However, the mechanisms involved are going to be relevant to all scientists studying cell biology whatever their disease or cell of interest. Some sections, however, would undoubtedly benefit from some or more simple diagrams or tables. Nevertheless this volume is a welcome addition to the series, although its topic and overall price will lead to a restricted market. It should be recommended for most medical libraries.—RS

NOTICES

2nd Central European Conference on Lung Cancer

The 2nd Central European Conference on Lung Cancer, under the auspices of the International Association for the Study of Lung Cancer, will take place on 13–16 April 1994 at the Congress Centre, Ljubljana, Slovenia. For further details contact: Professor Janez J Orel, Department of Thoracic Surgery, University Medical Centre, Zaloška 7, 61105 Ljubljana, Slovenia. Telephone: +38 61 317 582. Fax: +38 61 116 006.

IInd International Meeting in General Thoracic Surgery

The IInd International Meeting in General Thoracic Surgery will be held in Barcelona on 6 and 7 October 1994. For further information contact the Congress Secretariat, RCT asociados, Aulèstia i Pijoan 12 baixos, 08012 Barcelona, Spain. Telephone: 34-3-415 69 38. Fax: 34-3-415 69 04.

International Congress for Lung Cancer

The International Congress for Lung Cancer will be held on 22–26 June 1994. For further information contact Ms Poppy Katevati, Congress Manager, Olympic Sun SA, Athens, Greece. Telephone: 30-1-3230083. Fax: 30-1-3229194.

CORRECTIONS

Time course and duration of bronchodilatation with formoterol dry powder in patients with stable asthma

In the paper by A Wallin *et al* (June 1993;48:611–4) we regret an error on page 611 in the Results section of the Abstract, line 8 which should read "... was sustained for 6 hours and 16 minutes with salbutamol 400 µg ...".

Lung function in white children aged 4 to 19 years: II—Single breath analysis and plethysmography

In the paper by M Rosenthal *et al* (August 1993;48:803–8) the regression equation for VA in females (column F, table 2) on page 805 should read -7.669615×10^{-7} .