Salmeterol vs. Formoterol: A Comparison of Rapid Bronchodilator Effect in a Randomized Controlled Trial

NAMRATA SINGHANIA, RADHIKA DHAMIJA, R LODHA AND SK KABRA

From the Pediatric Pulmonology Division, Department of Pediatrics, All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110 029, India.

Correspondence to: Dr S. K. Kabra, Additional Professor, Department of Pediatrics, All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110 029, India. Email: skkabra@hotmail.com

Manuscript received: January 8, 2007; Initial review completed: June 12, 2007; Revision accepted: October 23, 2007.

ABSTRACT

We conducted this double blind randomized controlled trial to compare the rapid bronchodilator effect of salmeterol and formoterol in 60 children with stable asthma. Participants were randomized to receive either salmeterol (50 μg) (n=31) or formoterol (24 μg) (n=29) by metered dose inhaler and spacer. Spirometry was performed at baseline, at 30 minutes, and at 60 minutes. Bronchodilatation was assessed by changes in FEV_1 at 30 and 60 minutes. Baseline parameters were comparable in the two groups. There was no significant difference in the FEV_1 at 30 and 60 minutes between two groups. We conclude that salmeterol and formoterol both cause bronchodilator response at end of 60 minutes and are not different with regards to their rapid bronchodilator response.

Key words: *Childhood asthma, Formoterol, Long-acting beta-agonists, Salmeterol.*

INTRODUCTION

Inhaled corticosteroids (ICS) are the mainstay of long-term treatment of asthma. In moderate and severe persistent asthma, long acting beta-2 agonists (LABA) such as salmeterol and formoterol are added to ICS. Efficacy and safety of LABA has been demonstrated in children in long-term management of asthma(1-2). Studies done in adult asthmatics reveal a comparable bronchodilating and broncho-protective effects of the two drugs(3). However, there are no studies in children comparing rapid bronchodilator action of these two drugs. We conducted this trial to fill this void in literature.

METHODS

This double blind randomized controlled trial was carried out in Pediatric Chest Clinic (PCC) of a tertiary care hospital in north India. Children of either sex between ages of 5-15 years with moderate persistent asthma(4) were enrolled. Those with acute exacerbation of asthma or who had taken any bronchodilator drugs in last 24 hours were excluded. Informed consent was obtained from the parents.

Randomization was done by computer-generated numbers. For blinding, similar looking metered dose inhalers (MDIs) were labeled A, B, C, D, E, F; 3 of which contained salmeterol and 3 contained formoterol. As per random numbers patients were given drugs from these MDIs. The MDIs were purchased from market (Foratec and Serobid, Protec and Cipla India); a person not involved in the study evaluation removed the labels of drugs and put a sticker with label of A,B,C,D,E,F (3 formoterol and 3 salmeterol). Children received either salmeterol (50 microgram) or formoterol (24 microgram) by spacer. Participants were explained about the study, spirometry and inhalation of medicines with metered dose inhaler and spacer. Details of history and

physical examination including duration, severity of asthma and medications were recorded in a structured performa. A base-line spirometry was done using AutoSpiro portable spirometer. FVC, PEFR, FEV_1, FEF25 and FEF75 were recorded. Children were administered two actuations of study drug (salmeterol 25 μg/ actuation or formoterol 12 μg/ actuation) using metered dose inhaler and spacer. Children took at least 5 tidal breathing after each actuation of MDI. All clinical parameters and spirometry were repeated after 30 and 60 minutes of drug administration. Investigator collecting the data also asked for any adverse effect in form of tremors, nausea, vomiting, etc. before performing spirometry each time.

A sample size of 30 in each group was calculated to detect the difference in FEV_1 of more than 15% at 60 minutes with power of 80% and confidence level of 95%. All details were entered in Excel spread sheet and analyzed by STATA software (Stata Inc. College Station, TX) before breaking the code.

The baseline parameters between two groups were compared. Change in spirometric parameters was calculated and percentage increase in two groups was compared. Continuous variables were compared by applying '*t*' test and for discreet data chi square test was applied. A *P* value of <0.05 was considered significant.

RESULTS

A total of 60 children were enrolled in the study (***Fig.* 1**). The average age of children in two groups were similar (formoterol 9.7±3.1 years and salmeterol 9.6±3.1 years). The male to female ratio in formoterol group was 22:7 as compared to 16:15 in the salmeterol group (*P*=0.003). The baseline spirometric parameters were also comparable in the two groups.

There was significant increase in all the spirometric parameters within each group (***Table* I**). There was no significant difference between the two groups at baseline, 30 minutes and 60 minutes (***Table* I**). The percent increases in the spirometric parameters were also comparable in the 2 groups. Number of patients who had more than 12% increase in the FEV_1 from baseline to 30 and 60 minutes were 12 (41%) in formoterol and 17 (54%) in salmeterol group (*P*=0.3).

DISCUSSION

The present study aimed to compare rapid bronchodilator response of salmeterol and formoterol. We used maximum recommended doses of salmeterol and formoterol(5) to take care of dose response relationship that has been documented with formoterol(6). The rapid bronchodilator response in form of improvement in FEV_1 was measured at 0,30 and 60 minutes because the bronchodilator response of rapid acting bronchodilators is optimal at 30 minutes(7). The results suggested that there was no significant difference in the bronchodilator response in children between 5-15 years with stable asthma at 30 and 60 minutes.

There is no study in children that compares the two drugs. Avila-Castañón, *et al.*(8) in their double-blind, parallel-group study involving 36 adolescents comparing rapid bronchodilator response of salbutamol and formoterol reported that $\%FEV_1$

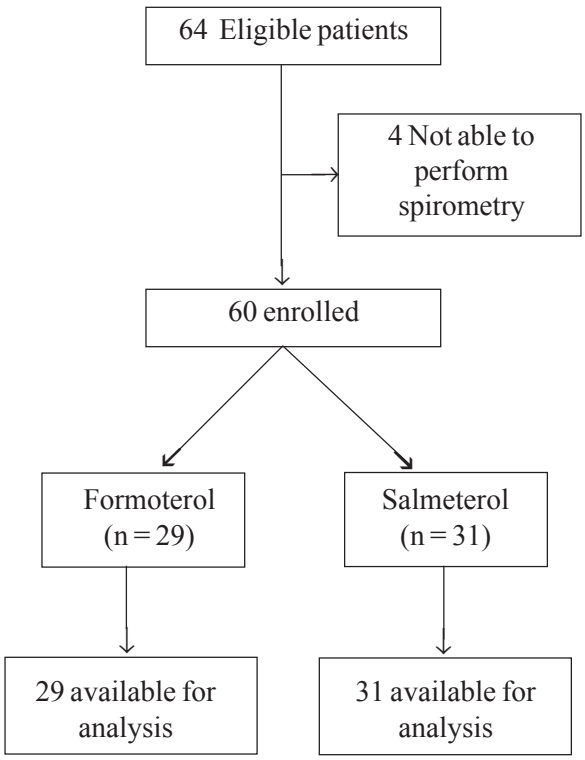

FIG. 1. *Study flow chart*

TABLE I BRONCHODILATOR RESPONSE TO FORMOTEROL AND SALMETEROL AT 30 AND 60 MINUTES.

Respiratory parameters	Formoterol group (*n*=29)	Salmoterol group (*n*=31)	*P*
FEV_1 (L) (Baseline)	1.02 (0.93-1.20)	0.85 (0.69-1.16)	0.78
FEV_1 (L) (30 min)	1.22 (1.04-1.52)	1.1 (0.67- 1.45)	0.52
FEV_1 (liters) (60 min)	1.28 (0.96-1.49)	1.08 (0.77-1.4)	0.86
% predicted FEV_1	55.2 (45.5-58.7)	50.2 (37.3-62.8)	0.58
% predicted FEV_1 (30 min)	59.93 (51.7-66.4)	59.04 (50.87-65.64)	0.99
% predicted FEV_1 (60 min)	59.41 (53.33-65.21)	63.6 (50.26-76.00)	0.48
FVC (liters) (Baseline)	1.31 (0.97-1.52)	1.08 (0,77-1.42)	0.34
FVC (liters) (30 min)	1.36 (1.19-1.66)	1.48 (0.81-1.71)	0.59
FVC (liters) (60 min)	1.5 (1.18-1.67)	1.38 (0.78-1.72)	0.88
% predicted FVC	60.2 (47.05-71.30)	58.2 (42.9-72.8)	0.91
% predicted FVC (30 min)	60.37 (51.39-71.06)	59.22 (51.47- 66.57)	0.98
% predicted FVC (60 min)	56.09 (50.92- 69.28)	60.19 (51.9- 72.81)	0.52
PEFR (L/ min) (Baseline)	180 (160-218)	147 (119-184)	0.93
PEFR (L/ min) (30 min)	219 (193-251)	159 (131-233)	0.03
PEFR (L/ min) (60 min)	219 (166-232)	173 (141-231)	0.26
% predicted PEFR	60 (57.6-67.8)	62 (52-72)	0.97
% predicted PEFR (30 min)	74 (68-78)	66 (60-80)	0.27
% predicted PEFR (60 min)	69 (62-79)	75 (62-82)	0.46

Values are median (95% confidence interval); FEV_1: Forced expiratory volume in first second, FVC: Forced vital capacity, PEFR: Peak expiratory flow rate

values at 3, 30 and 60 minutes were similar in both groups suggesting rapid onset of action of formoterol. Ferrari, *et al*.(9) in their double-blind, two-period cross-over study comparing salmeterol and formoterol on 11 adults with exercise induced bronchoconstriction (EIB) (mean age 21.2 years) demonstrated that formoterol provided significantly better protection against EIB than salmeterol at 30 minutes.

We do not have ready explanations for our findings. Possible reasons for no difference in rapid bronchodilator response in our study may be less severe bronchospasm. It has been reported that rapid bronchodilator response with formoterol was more when there was severe exacerbation with FEV_1 less than 50% predicted(10). We included stable asthmatics only. Beta 2 AR polymorphism has been suggested as one of the reason for difference in the response to both LABA(11).

The major limitation of this study was that we did not measure FEV_1 before 30 minutes. The onset of bronchodilator action of formoterol has been demonstrated to be three minutes (8). Measurement before 30 minutes and longer follow up after 60 minute might have given better idea about the trends in rapid bronchodilator response of LABA.

Contributors: SKK and RL: Designed study, helped in data collection and analysis, and manuscript writing. Will act as guarantor for the paper. NS and RD: designed the study, collected data and helped in data analysis.

Competing interest: None.

Funding: None stated.

REFERENCES

1. Boner AL, Spezia E, Piovesan P, Chiocca E, Maiocchi G. Inhaled formoterol in the prevention of exercise-induced bronchoconstriction in asthmatic children. Am J Respir Crit Care Med 1994; 149: 935-939.

WHAT THIS STUDY ADDS?

- There is no significant difference in rapid bronchodilation effect between salmeterol and formoterol in stable asthmatic children in age group of 5-15 years.

2. Russell G, Williams DA, Weller P, Price JF. Salmeterol xinafoate in children on high dose inhaled steroids. Ann Allergy Asthma Immunol 1995; 75: 423-428.
3. Palmqvist M, Persson G, Lazer L, Rosenborg J, Larsson P, Lotvall J. Inhaled dry-powder formoterol and salmeterol in asthmatic patients: onset of action, duration of effect and potency. Eur Respir J 1997; 10: 2484-2489.
4. British Thoracic Society; Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma. Thorax 2003; 58 (Suppl 1): i1-94.
5. von Berg A, Berdel D. Efficacy of formoterol metered aerosol in children. Lung 1990;168 Suppl: 90-98.
6. Pohunek P, Matulka M, Rybnicek O, Kopriva F, Honomichlova H, Svobodova T. Dose-related efficacy and safety of formoterol (Oxis) Turbuhaler compared with salmeterol Diskhaler in children with asthma. Pediatr Allergy Immunol 2004; 15: 32-39.
7. Scalabrin DM, Naspitz CK. Efficacy and side effects of salbutamol in acute asthma in children: comparison of oral route and two different nebulizer systems. J Asthma 1993; 30: 51-59.
8. Avila-Castañón L, Casas-Becerra B, Del Río-Navarro BE, Velázquez-Armenta Y, Sienra-Monge JJ. Formoterol vs. albuterol administered via Turbuhaler system in the emergency treatment of acute asthma in children. Allergol Immunopathol (Madr) 2004; 32: 18-20.
9. Ferrari M, Segattini C, Zanon R, Bertaiola M, Balestreri F, Brotto E, *et al.* Comparison of the protective effect of formoterol and of salmeterol against exercise-induced bronchospasm when given immediately before a cycloergometric test. Respiration 2002; 69: 509-512.
10. Ulrik CS, Kok-Jensen A. Different bronchodilating effect of salmeterol and formoterol in an adult asthmatic. Eur Respir J 1994; 7: 1003-1005.
11. Hall IP. Beta 2-adrenoceptor polymorphisms and asthma. Clin Exp Allergy 1999; 29: 1151-1154.