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Irma Douglas Gomez, Marilia de Dirceu Silva, Maria Poliana Bueno, Dirceu Solé, Charles Kirov Naspitz

Protective effects of different doses of inhaled fenoterol on methacholine-induced bronchoconstriction in asthmatic children

Division of Allergy, Clinical Immunology and Rheumatology Department of Pediatrics Universidade Federal de São Paulo - Escola Paulista de Medicina, São Paulo, Brazil

Objective: To evaluate the protective effect of different doses of inhaled fenoterol (F) on bronchoconstriction induced by methacholine (M). **Design:** randomized double-blind study. **Setting:** Referrence center. **Participants:** 9 children (aged from 7 to 15 years old), with mild or moderate asthma and allergic to *D. pteronyssinus*. **Intervention:** On the first day, the M concentration necessary to induce a 20% fall in the forced expiratory volume in the first second (FEV_1; $PC_{20}FEV_1$) was determined using closed circuit inhalation (De Vilbiss 646). On subsequent days, the children inhaled a dose of F (25 or 50 or 100 or 200 mg) through the same circuit and, after 15 minutes the FEV_1 was measured, becoming the basal value. Bronchoprovocation was then initiated using the concentration prior to the $PC_{20}FEV_1$ of the first day and continuing until there was a 20% fall in the FEV_1. This concentration was the "new" $PC_{20}FEV_1$. **Results:** F in a dose of 25 mg protected 2 of the 9 children, in a dose of 50 mg protected 4 of the 9 and in doses of 100 and 200 mg protected all children. We did not observe any relationship between the magnitude of the bronchodilation and bronchoprotection induced by the inhalation of F. **Conclusions:** Our results suggest that a dose of 100 mg of F is capable of inducing bronchoprotection in children with mild/moderate asthma.

Uniterms: Asthma. Children. Bronchial hyperreactivity. Beta agonists. Fenoterol. Methacholine.

INTRODUCTION

Inhaled short-acting beta 2 agonists constitute the first choice medication for the treatment of acute asthma flares and in preventing bronchospasms induced by exercise.[1-5] One of the most widely used in Brazil is fenoterol in solution form for nebulization. It is also available as a metered dose inhaler (MDI) in doses of 100 and 200 mg /puff. Previous studies have tried to relate its use to the increase in asthma mortality, which we did not observe in a previous study[6] and was not confirmed by a meta-analysis study.[7]

Previous studies have shown that fenoterol is capable of blocking the bronchospasm induced by the inhalation of histamine[8-12] and methacholine[8,9] and also protect against exercise-induced asthma (EIA).[13] A 50 mg dose was enough to avoid EIA[13] and 10 mg avoided brocho-constriction caused by inhaled histamine.[12]

In this study we evaluate the capacity of inhaled fenoterol for the protection of methacholine-induced bronchospasm in Brazilian atopic asthmatic children.

Address for correspondence:
Dirceu Solé
Av. Paes de Barros, 844 ap. 61
São Paulo/SP - Brasil - 03114-000

METHODS

Nine children, from 7 to 15 years of age (6 boys), with mild or moderate atopic asthma,[1] took part in this study. The atopic status was characterized by a positive skin prick test to *Dermatophagoides pteronyssinus.* All the children were able to perform espirometric measurements in an appropriate manner.[14] This study was approved by the UNIFESP-EPM Ethical Committee and the children were enrolled after their parents gave informed consent.

The patients were submitted to bronchoprovocation (BPT) with methacholine according to the method standardized in our Division by Mallozi et al.,[15] and modified from Chai et al.[16] Upon being included in the study, the exclusion intervals of the following drugs were observed: short-acting beta 2 agonists and aminophylline, 8 hours; ipratropium bromide, 12 hours; slow-releasing theophylline, 24 hours; classic antihistamines, 7 days; non-classic antihistamines, 15 days; disodium chromoglycate, 15 days; oral and inhaled corticosteroids, 30 days.

Five BPT's were carried out, always in the morning, interspersed with a day of rest. All patients were asymptomatic and FEV_1 was greater than or equal to 80% of the predicted normal values.[17]

At the first BPT the methacholine $PC_{20}FEV_1$ (concentration of methacholine capable of inducing a 20% fall in the FEV_1 baseline value) was established. For this BPT, the methacholine was inhaled in increasing concentrations (0.025; 0.25; 1.0; 2.5; 10.0 and 25.0 mg/mL) until a fall in the FEV_1 took place, greater or equal to 20% of the baseline value. The methacholine $PC_{20}FEV_1$ calculation was extrapolated using monolog graph paper.

On subsequent days the patients inhaled fenoterol 15 minutes before the BPT was carried out. The fenoterol was administered using the same inhalation closed circuit (De Vilbiss 646) and 0_2 (5L/min) in different concentrations each day, distributed using the randomized double-blind method (25 mg, 50 mg, 100 mg and 200 mg).

The BPT's were started after the child had inhaled saline solution to obtain the baseline FEV_1. Fenoterol was then inhaled and 15 minutes later, another FEV_1 was obtained which became the basal value for the remainder of the test. The BPT began with the inhalation of the previous concentration of methacholine necessary to obtain the initial $PC_{20}FEV_1$, followed by larger doses until the 20% fall in the FEV_1 was obtained, establishing a new methacholine $PC_{20}FEV_1$ for each dose of inhaled fenoterol. The $PC_{20}FEV_1$ with values in excess of 38.78 mg/mL were considered to be equal to 40.0 mg/mL.

The methacholine $PC_{20}FEV_1$ were expressed in mg/mL for each inhaled fenoterol concentration and in relation to the value obtained during the first provocation, by simple division. To analyse the results, non-parametric tests were used (Friedman, Fisher) considering the null hypothesis rejection level at 5%.

RESULTS

All the children underwent the BPT without presenting any adverse effects. The initial $PC_{20}FEV_1$ of all of them was equal to or less than 8 mg/mL. The analysis of the various $PC_{20}FEV_1$ observations showed values significantly higher than baseline after inhalation of 100 and 200 mg of fenoterol (Table 1).

Table 1
$PC_{20}FEV_1$ methacholine values after inhalation of different doses of fenoterol.

Child	Baseline (a)	25 mg (b)	50 mg (c)	100 mg (d)	200 mg (e)
1	3.27	3.55	19.50	7.30	7.30
2	0.10	0.008	0.09	0.36	0.35
3	0.0215	0.68	0.63	1.55	5.70
4	3.77	3.77	4.45	16.00	18.40
5	6.75	14.45	15.45	36.50	> 38.78
6	5.90	5.60	9.20	> 38.78	> 38.78
7	8.00	10.00	15.00	> 38.78	> 38.78
8	0.36	0.13	1.275	3.20	5.00
9	1.85	0.42	1.30	6.00	6.40
Mean	3.36	4.29	7.43	16.77	18.13

Friedman: H calculated = 27.727* *p < 0.05
Dunn: a,b < d,e

Table 2
Ratio between the $PC_{20}FEV_1$ methacholine before and after inhalation of different doses of fenoterol.

Child	25 mg (b)	50 mg (c)	100 mg (d)	200 mg (e)
1	1.08	5.96	2.23	2.23
2	0.08	0.90	3.60	3.50
3	31.60	29.30	72.00	265.10
4	1.00	1.18	4.20	4.88
5	2.14	2.29	5.40	5.90
6	0.95	1.60	6.78	6.80
7	1.23	1.90	5.00	5.00
8	0.36	3.54	8.90	13.89
9	0.22	0.70	3.24	3.46
Mean 4.30	5.26	12.37	34.53	

Friedman: H calculated = 21.068* *p < 0.05
Dunn: b < d, e c > e

The ratio between the two $PC_{20}FEV_1$ values, obtained before and after protection using the four inhaled doses is shown in Table 2. Considering a ratio of at least 2 (doubling dose) as a positive value, the mean ratio after inhalation of 25 mg of fenoterol was 4.3. However, only 2 patients were in fact protected. The same result was observed with the 50 mg dose; in this case 4 of the 9 patients were protected (p= 0.3147). With the 100 and 200 mg concentrations all the patients were protected.

The response to the inhalation of different doses of fenoterol showed, after 15 minutes, a similar increase (9 to 12%) in the FEV_1 values, with no significant differences.

DISCUSSION

Short-acting beta 2 agonists, because of their bronchodilating effect, are widely used in treating acute exacerbations of asthma and in the prevention of EIA.

The continuous use of these agents has been associated with a deterioration in the control of asthma and with mortality.[18,19] The main causes for these possible effects have not been clarified yet and are still unknown, but have been related to inhaled drugs, especially via metered dose inhaler.[20]

Worsening of asthma was not proved in recent studies.[21,22] These studies showed that the regular use of inhaled short-acting beta 2 agonists cause neither harmful nor beneficial effects in the control of asthmatic patients. Thus, the recommendation is that these drugs be used only when necessary, although when an individual patient has better control of the asthma with continuous use, this treatment should not be discarded.[21]

Several asthma management guidelines[1-5] recommend the use of beta 2 agonists only as needed (for acute episodes). Larger doses than recommended for inhaled beta 2 agonists are not necessary for obtaining the same bronchodilation: the occasional side effects are dose-related.[1-5]

Our study shows that there may be a protective bronchodilating effect using much smaller doses of fenoterol, such as 25 and 50 mg, but which do not protect all patients. This fact was observed with a minimum protective dose of 100 mg which, for individual patients, can be evaluated using 25 and 50 mg doses.

Although we evaluated the protective dose of fenoterol needed to protect against methacholine-induced bronchospasm, it seems reasonable to recommend the dose of 100 mg of fenoterol as the initial dose for treatment of an acute attack of asthma.

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RESUMO

Objetivos: Avaliar o efeito protetor de diferentes doses de fenoterol (F) inalado sobre a broncoconstrição induzida por metacolina (M). **Tipo de Estudo:** estudo duplo-cego e randomizado. **Local:** Centro de referência. **Participantes:** Nove crianças (7 a 15 anos) com asma leve ou moderada, alérgicas ao *D. pteronyssinus.* **Intervenção:** As doses de F (25 ou 50 ou 100 ou 200 mg) foram administradas por inalação com circuito fechado (De Vilbiss 646). No primeiro dia determinou-se a concentração de M capaz de induzir queda de 20% nos valores de VEF_1 ($CP_{20}VEF_1$). Nos dias subseqüentes, inalavam a dose de F pelo mesmo circuito medindo o VEF_1 15 minutos após (referência). A seguir iniciavam a broncoprovocação pela concentração anterior à da $CP_{20}VEF_1$ do primeiro dia e prosseguiam até que houvesse queda de 20% no valor do VEF_1 para a determinação do novo $CP_{20}VEF_1$. **Resultados:** O F inalado na dose de 25 mg protegeu 2/9 crianças e na de 50 mg houve proteção de 4/9 crianças. Todos os pacientes foram protegidos com as doses de 100 e 200 mg. Não observamos relação entre a magnitude da broncodilatação e broncoproteção induzidas pela inalação do F. **Conclusões:** Nossos resultados sugerem que a dose de 100 mg de F é protetora da broncoconstrição em crianças com asma leve/moderada.