

REVIEW ARTICLE

Pressurised metered-dose inhalers (MDIs) versus dry powder inhalers devices (DPIs) to rapid-acting inhaled β_2 -agonists for asthma in children

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SUMMARY

Objective: To compare the clinical effectiveness of pressurized metered-dose inhalers (MDIs) with that of dry powder inhalers (DPIs) in delivering short-acting β_2 -agonists in children with asthma.

Methods: Searches were performed in Medline (1997-March 2002), the Cochrane Library Database and the Embase reference lists of review articles and clinical trials. In addition, the international headquarters of β_2 -agonist manufacturers were contacted. We performed a review of randomized controlled trials.

Results: Ten randomized controlled trials were included. No differences in clinical effectiveness were found between MDIs and PDIs. Two studies reported that fewer adverse events occurred when the Turbuhaler was used. Two long-term studies in children found that children preferred the MDI to the Rotohaler.

Conclusions: 1) In stable asthma, short-acting β_2 bronchodilators in standard MDIs are as effective as dry powder inhalers. 2) Pooling of results was limited by the small number of studies and therefore no overall conclusions could be drawn. 3) From the limited data available, we found little or no evidence for an additional clinical benefit of DPI devices over standard MDIs in children with asthma.

Key words: Metered-dose inhalers. Dry powder inhalers. Terbutaline. Albuterol. Salbutamol. Asthma. Children.

INTRODUCTION

Recently published guidelines for the investigation and management of chronic asthma have emphasised the importance of bronchodilator therapy in this disease. Reliever medications that act quickly to relieve bronchoconstriction in asthma and its accompanying acute symptoms include rapid-acting inhaled β_2 -agonists.

Rapid-acting inhaled β_2 -agonists provide rapid relief of symptoms and include salbutamol (albuterol), terbutaline, fenoterol, and reproterol. Formoterol and salmeterol has both a rapid onset and a long duration of action. Like other β_2 -agonists, they relax airway smooth muscle, enhance mucociliary clearance, decrease vascular permeability, and may modulate mediator release from mast cells (1).

Therapy with rapid-acting inhaled β_2 -agonists is comparable to, or better than, oral therapy in producing bronchodilatation and avoiding side effects (2).

A number of different inhaler devices are available to deliver β_2 -agonist bronchodilators in asthma. These include pressurised metered-dose inhalers (MDIs) and dry powder inhalers devices (DPIs).

MATERIAL AND METHODS

We searched Medline (1997-march 2002), Data Base of Cochrane Library³, Embase, reference lists of review articles and clinical trials, and contacted international headquarters of β_2 -agonists manufacturers. Register was searched on all fields for: (inhaler [All Fields] OR accuhaler [All Fields] OR aerochamber [All Fields] OR autohaler [All Fields] OR chamber [All Fields] OR diskhaler [All Fields] OR extension [All Fields] OR fisonair [All Fields] OR nebuhaler [All Fields] OR spacer [All Fields] OR spacing device [All Fields] OR volumatic [All Fields] OR turbuhaler [All Fields] OR turbuhaler [All Fields] OR rothaler [All Fields] OR dry powder [All Fields] OR MDI [All Fields] OR DPI [All Fields]) AND (albuterol [All Fields] OR bricanyl [All Fields] OR fenoterol [All Fields] OR reproterol [All Fields] OR salbutamol [All Fields] OR terbutaline [All Fields] OR ventolin [All Fields] OR) AND (children [All Fields]).

RESULTS

We included only randomised controlled trials of short acting β_2 -agonists in children. Ten trials met inclusion criteria and were published in full-text.

1. MDI vs Turbuhaler (containing terbutaline or salbutamol)

1.1. Preference for inhaler device

Fifty-seven children with asthma participated in the clinical trial of Hultquist et al.⁴, to compare the clinical effect and acceptance of terbutaline sulphate via Turbuhaler with that of metered-dose inhaler (MDI). The trial consisted of two parts. In the first part of the study, which made use of a double-blind cross-over design, the clinical effect and number of treatment occasions with Turbuhaler were compared with those of MDI. In the second part, which was open, all patients were treated with Turbuhaler for 2 weeks. At the end of this period the patients were asked to make a subjective assessment of effect and to state their preference. There was no difference in clinical effect and number of treatment occasions between Turbuhaler and MDI. A majority of the patients thought Turbuhaler had the best effect and was easy to use.

Ahlstrom et al (5) compared Turbuhaler with a pressurized metered-dose inhaler, attached to a Nebuhaler. The study had an open, cross-over randomized design. Each treatment period consisted

of 2 weeks. Diary cards were filled in every morning and evening by the parents regarding PEF, asthma symptoms, extra inhalations of terbutaline, and side effects. Twenty-one children (mean age 3.9 years) were included in the study. A highly significant ($P < 0.001$) increase in peak expiratory flow (PEF) was obtained after inhalation with both devices. The PEF values in the mornings after inhalation of terbutaline with Turbuhaler were significantly higher ($P = 0.046$) than those with Nebuhaler. Further, the PEF baseline values in the evenings before inhalation were also significantly higher ($p = 0.03$) with Turbuhaler. No difference was found in asthma symptoms and extra medication between the two devices. The parents found Turbuhaler easier to handle and 19 of 21 preferred this device for future use.

1.2. Adverse events

Two studies (5, 6) in 68 patients showed that there were less adverse events with the use of Turbuhaler compared to the pMDI (RR 0.12; 95 %CI 0.02,0.61).

In the study of Ahlstrom et al (5) side effects were mild and few with both devices.

Thirteen children with asthma were treated for Fuglsang et al (6) with cumulative doses of terbutaline delivered as a pressurized aerosol and Turbuhaler in a randomized cross-over dose-response study. The cumulative dose of terbutaline was 2 mg on each study day. All children used a correct aerosol inhalation technique. At no time was there any difference in forced expiratory volume in 1 s (FEV_1), forced midexpiratory flow, forced vital capacity, peak expiratory flow rate, or percent increase in these parameters between the two inhalers. The mean total increases in FEV_1 after 2 mg of terbutaline were 60 % (aerosol) and 62 % (Turbuhaler); 90 % of these increases were measured after a cumulative dose of 0.5 mg terbutaline. One milligram of terbutaline inhaled from a Nebuhaler at the end of each study day did not result in additional increase of pulmonary functions, indicating that maximal bronchodilation had been achieved with both inhalers. After a cumulative dose of 2 mg terbutaline from the aerosol seven, children complained of tremor and one of restlessness. No side effects were reported when the Turbuhaler was used ($p < 0.02$).

1.3. Other studies

Laberge et al (7) compared the bronchodilator response of terbutaline delivered either by a dry powder inhaler, the Turbuhaler, or by a metered-dose inhaler attached to a Nebuhaler inhaler in 10 children with stable asthma who were 3 to 6 years of age. The bronchodilator response did not differ between the two inhalational devices.

One hundred and eighteen asthmatics (aged range 8-15, mean age 11,3) with bronchial obstruction (mean Vmax 50 % : 59.5 % pred, SD 17.8 % pred) were studied⁸ and allocated at random to two groups of 59 patients to inhale 0.5 mg of terbutaline either by Turbuhaler or by MDI (and placebo by dummy of the other device). In expiratory spirometry and bodyplethysmography were conducted before and 10 min after inhalation. Bronchodilation was effective [change in airways resistance (delta RAW) -50 %, change in forced expiratory volume in 1 s (delta FEV₁) + 15 %, delta Vmax 50 % or 25 % + 25 % of baseline] in 41 of 59 patients with MDI (69.5 %) and 33 of 59 patients with Turbuhaler (55.9 %). The effect on Vmax 50 % was significantly better with MDI than with Turbuhaler. Turbuhaler users with higher inspiratory flow [forced inspiratory volume in 1 s (FIV1), forced inspiratory flow at 50 % vital capacity (FIF50)] reached better bronchodilation, while bronchodilatory effect was not correlated with inspiratory performance in MDI users. Peak inspiratory flow (PIF) did not correlate well with bronchodilation by Turbuhaler. When using Turbuhaler for bronchodilation, the effectiveness of terbutaline depends upon the degree of inspiratory capacity. This can lead to impaired bronchodilatory effect in subgroups of obstructive young asthmatics with low inspiratory flow. In contrast, when using a MDI, inspiratory capacity does not seem to influence the effectiveness of terbutaline.

Razzouk et al (9) compare the efficacy of single doses of salbutamol Turbuhaler (50 and 100 microg), salbutamol pressurized metered-dose inhaler (pMDI) (100 microg) and placebo in children with stable chronic reversible airway obstruction. Primary efficacy variable (FEV₁-av) was calculated as the area under the curve of forced expiratory volume in one second (FEV₁) (AUC, 0-4 h) and divided by the observed time. The study was of a randomized, single-dose, cross-over and double-blind design. Seven centres participated. FEV₁ was measured pre-dose and at 15 min, 0.5, 1, 1.5, 2, 3 and 4 h post study dose. Forty asthmatic children with a mean age of 9 years (range: 6-12), mean FEV₁ of 1.6 l (range: 0.9-2.4) and a mean FEV₁ in percentage of

predicted normal value of 80 % (range: 61-109) were randomized into the study. The mean reversibility 30 min after inhaling 2 x 100 microg salbutamol from MDI was 20 % (range: 9-45) or 15 % (range: 8-27) in percentage of predicted normal value. The mean FEV₁-av was 1.63 l for placebo, 1.71 l for 50 microg salbutamol Turbuhaler, 1.76 l for 100 microg of salbutamol Turbuhaler and 1.76 for 100 microg salbutamol MDI. Corresponding values for maximum FEV₁ were 1.76, 1.85, 1.87 and 1.87 l, respectively. There were no statistically significant differences between the active treatments in FEV₁-av or maximum FEV₁. All active treatments were significantly better than placebo.

Svenonius et al (10) compared the bronchodilating effect of inhalation from the Turbuhaler (0.5 mg terbutaline x 2) with the effect of inhalation from the MDI (0.25 mg terbutaline x 4) in 12 children aged 9-17 years with reproducible, exercise-induced asthma. The treatments were given on two occasions, 5 min apart (terbutaline 0.5 mg + 0.5 mg). The study was performed as a double-blind, double-dummy, and placebo-controlled trial. The study was conducted on three separate days. The bronchoconstriction was induced by steady running on a treadmill. Forced expiratory volume in 1 s (FEV₁), vital capacity (VC), and volume of trapped gas (VTG) were measured before and after the exercise test and after treatment. The study showed that the same amount of terbutaline inhaled from the Turbuhaler or from a MDI is equally effective for reversing exercise-induced asthma, and that the Turbuhaler is possibly more effective for treating spasm in small airways.

2. MDI vs Rotahaler (containing salbutamol)

2.1. Preference for inhaler device and adverse events

One 12 week parallel study in 204 children, age 4 to 12 years (mean age 8,2 years), showed that children preferred the MDI almost twice more often than the Rotahaler (RR 1.69; 95 %CI 1.14,2.51) (11). Studies were double-blind and placebo-controlled with randomized assignment to treatment. The dose-ranging study in 30 patients indicated that similar single doses of albuterol aerosol and powder had comparable effects with the intermediate doses (i.e., 180 micrograms of aerosol and 200 micrograms of powder) providing effective bronchodilation with minimal adverse effects. In the subsequent 12-week, parallel-group study, 204 children received albuterol as either aerosol, 180 micrograms, or

powder, 200 micrograms four times a day. Both formulations were equally effective with no untoward cardiovascular effects and only one incident of mild tremor. Among those children who expressed a preference for one of the delivery systems, significantly more children preferred the powder (44 % versus 26 %, $p < 0.01$).

Croner et al (12) reported in their 4 week cross-over study of 43 patients (3-16 years of age, mean 9,6) that more children preferred that pMDI than the Rotahaler (RR 2.67; 95 % CI 1.22,5.81). Is a double-blind cross-over study on the clinical effect of inhaled salbutamol powder (0.2 mg/dosis) compared with spray (0.1 mg/dosis) over two 4-week periods. Both administrations gave significant improvement in air flow meter (AFM) results. There was no significant difference between the periods on active powder or spray regarding daily symptom scores, adjuvant medication or AFM values. The powder caused cough in four children but in 12 of 28 children it was considered as easy or easier to accept as the spray; nine of these 12 children were younger than 10 years of age.

2.2. Other studies

One 4 week cross-over study in 86 patients (12) showed that daily PEFR was greater by 105 L/min when using the Rotahaler as opposed to the MDI (WMD 105.40; 95 %CI 59.99,150.81). However, this study design used a 2:1 ratio for the dose of salbutamol, where the Rotahaler provided 200mcg per puff and the MDI provided 100 μ g per puff. Children were instructed to take 3-6 puffs from each device per day according to their need and the dose used was recorded on a diary card. It is possible that the increased PEFR seen with the Rotahaler could be a result of the higher dose.

Forty-six patients aged 4-11 years (mean age 8 years) with asthma and exercise-induced bronchospasm were enrolled in this randomized, double-blind, single-dose, three-way cross-over study comparing albuterol aerosol, albuterol powder (Rotahaler), and placebo¹³. Exercise challenge was performed at the screening visit for qualifying and baseline determinations of pulmonary function and then 15 min after drug administration at each of three visits. Prevention of exercise-induced bronchospasm was assessed by comparing across all treatment groups the percentage change in FEV₁ from pre- to post-exercise, the percentage of patients protected by treatment, post-exercise minimum FEV₁, and post-exercise change in FEV₁. Safety was assessed by observation of clinical

adverse events, laboratory tests, physical examination, electrocardiogram and rhythm strips, vital signs, and pulmonary auscultation. Forty-four patients completed the study. Mean post-exercise FEV₁ decreased 6 % from pre-exercise values when patients were treated with either albuterol formulation; FEV₁ decreased 23 % when patients were treated with placebo. Exercise-induced bronchospasm was prevented in 95 % of patients when treated with albuterol powder, in 91 % treated with albuterol aerosol, and in 57 % treated with placebo. Patients maintained significantly higher mean minimum FEV₁ values after treatment with albuterol powder and albuterol aerosol than when treated with placebo. Treatment with either albuterol formulation produced a significantly smaller decrease in mean FEV₁ from pre- to post-exercise than treatment with placebo. No drug-related adverse events were reported.

One 12 week parallel study in 204 patients (11) reported a significant reduction in the number of acute exacerbations that required medical intervention using the Rotahaler device compared to pMDI (RR 0.52; 95 %CI 0.28,0.95).

CONCLUSIONS

1. In stable asthma, short-acting beta-2 bronchodilators in standard MDI's are as effective as dry powder inhalers.
2. The small number of children's studies allowed limited pooling of results so no overall conclusions could be drawn.
3. From the limited data available, this review could find little or no evidence for additional clinical benefit of DPI devices over a standard MDI for children with stable asthma.

RESUMEN

Objetivo: Determinar la efectividad de los aerosoles presurizados (MDIs) comparados con los dispositivos de polvo seco (DPIs), para liberar β_2 agonistas de corta acción en niños asmáticos.

Métodos: Se realizó una búsqueda bibliográfica en las bases de datos MEDLINE (1997-marzo 2002), base de datos de la Cochrane Library y EMBASE, buscando referencias de artículos de revisión y ensayos clínicos, y se contactó con las centrales internacionales de los productores de β_2 agonistas. Se hizo una revisión de ensayos controlados y aleatorios.

Resultados: Se incluyeron 10 ensayos controlados y aleatorios. No se encontraron diferencias entre los MDIs y DPIS en cuanto a efectividad clínica. Dos estudios mostraron un descenso de efectos adversos con el uso del Turbuhaler. Dos estudios a largo plazo en niños mostraron que los niños preferían el MDI comparado con el Rotahaler.

Conclusiones: 1) En el asma estable, los beta2 agonistas de corta acción en estándar MDI son tan efectivos como los DPIS. 2) El pequeño número de estudios en niños no permite obtener conclusiones definitivas. 3) De los limitados datos disponibles, en esta revisión se encuentra poca o ninguna evidencia, de que exista un beneficio adicional en la utilización de DPIS sobre estándar MDI en niños con asma.

Palabras clave: MDI. DPI. Terbutalina. Albuterol. Salbutamol. Asma. Niños.

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