

Original article

Regular vs prn nebulized treatment in wheeze preschool children

Background: International guidelines recommend regular treatment with inhaled glucocorticoids for children with frequent wheezing; however, prn inhaled bronchodilator alone or in combination with glucocorticoid is also often used in practice. We aimed to evaluate whether regular nebulized glucocorticoid plus a prn bronchodilator or a prn nebulized bronchodilator/glucocorticoid combination is more effective than prn bronchodilator alone in preschool children with frequent wheeze.

Methods: Double-blind, double-dummy, randomized, parallel-group trial. After a 2-week run-in period, 276 symptomatic children with frequent wheeze, aged 1–4 years, were randomly assigned to three groups for a 3-month nebulized treatment: (1) 400 µg beclomethasone bid plus 2500 µg salbutamol prn; (2) placebo bid plus 800 µg beclomethasone/1600 µg salbutamol combination prn; (3) placebo bid plus 2500 µg salbutamol prn. The percentage of symptom-free days was the primary outcome measure. Secondary outcomes included symptom scores, use of relief medication and exacerbation frequency.

Results: As compared with prn salbutamol (61.0 ± 24.83 [SD]), the percentage of symptom-free days was higher with regular beclomethasone (69.6%, SD 20.89; $P = 0.034$) but not with prn combination (64.9%, SD 24.74). Results were no different in children with or without risk factors for developing persistent asthma. The effect of prn combination was no different from that of regular beclomethasone on the primary and on several important secondary outcomes.

Conclusions: Regular inhaled glucocorticoid is the most effective treatment for frequent wheezing in preschool children. However, prn bronchodilator/glucocorticoid combination might be an alternative option, but it requires further study.

A. Papi¹, G. Nicolini², E. Baraldi³, A. L. Boner⁴, R. Cutrera⁵, G. A. Rossi⁶, L. M. Fabbri⁷, on behalf of the BEclomethasone and Salbutamol Treatment (BEST) for Children Study Group

¹Department of Respiratory Diseases, Research Center on Asthma and COPD, University of Ferrara, Ferrara, Italy; ²Medical Department, Chiesi Farmaceutici, Parma, Italy; ³Department of Pediatrics, Unit of Allergy and Respiratory Medicine, University of Padova, Padova, Italy; ⁴Department of Pediatrics, University of Verona, Verona, Italy; ⁵Respiratory Unit, Department of Pediatrics, Ospedale Pediatrico Bambino Gesù, Rome, Italy; ⁶Department of Pediatrics, Ospedale Gaslini, Genova, Italy; ⁷Department of Respiratory Diseases, University of Modena and Reggio Emilia, Modena, Italy

Key words: asthma; as needed; beclomethasone; salbutamol; wheezing.

L. M. Fabbri
Department of Respiratory Diseases
University of Modena and Reggio Emilia
Via del Pozzo, 71
41100 Modena
Italy

Accepted for publication 28 May 2009

Frequent wheezing occurs in a large proportion of preschool children and is mainly related to viral infections or to multiple triggers (such as exercise and exposure to smoke, allergens, or cold air, as well as viral infections) (1–3). Several phenotypes of preschool wheezing disorders have been recognized in epidemiologic studies (4), but they are of little clinical use as they may overlap and change over time making diagnosis and assessment of severity difficult (3).

Because of the heterogeneous nature of wheezing, there is no consensus on the definition of different phenotypes of preschool wheeze disorders and on their treatment (3, 5) as reflected in national and international guidelines recommendations (6, 7). Regular inhaled glucocorticoids have been shown to reduce symptoms in some studies (8–10) but not in others (11, 12). Intermittent treatment with

either inhaled or systemic glucocorticoids has been tested in recent trials with conflicting results (13–16).

Despite guidelines, these children are often treated on a prn basis according to the frequency and severity of symptoms (1, 2, 17). This is partly because of concerns about prolonged treatment with inhaled glucocorticoids (6, 7), considering that there is no evidence of any effect of prolonged treatments on the natural course of the disease (10, 18).

None of the guideline mentions the use of a prn combination of a rapid acting bronchodilator and a glucocorticoid, a treatment used in practice but never properly investigated (19, 20). In adults with mild persistent asthma, an inhaled prn short-acting bronchodilator/glucocorticoid combination is as effective as regular inhaled glucocorticoid (21).

We conducted a randomized, double-blind, double-dummy, placebo controlled clinical trial to determine whether regular nebulized glucocorticoid plus a prn bronchodilator or the simple prn use of a nebulized bronchodilator/glucocorticoid combination and no regular treatment is more effective than a prn bronchodilator alone in preschool children with frequent wheezing.

Methods

Study design

This multicenter, randomized, parallel-group, three-group, double-blind, double-dummy, placebo-controlled study began in March 2006 and ended in January 2007. Eligible children entered a 2-week prospective open run-in period during which they received only nebulized placebo bid plus 2500 µg prn nebulized salbutamol for symptom relief. Patients entered a 12-week double-blind treatment phase if they had wheeze and/or cough, and/or shortness of breath, and/or required relief medication on at least 7 days of the 2-week run-in period. We used a 2:1 treatment-to-placebo randomization ratio to expose fewer patients to placebo.

The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Independent ethics committees approved the study protocol, patient information sheet, and consent forms. A parent or guardian of each patient provided written informed consent.

Patients

We enrolled children aged 1–4 years with frequent wheezing defined as a documented history of at least three episodes of wheezing requiring medical attention in the previous 6 months (10).

The study was conducted in 19 pediatric specialist care units (investigators are acknowledged at the end of the paper). Preschool children with frequent wheeze who were referred to the centers because of a further episode of wheezing (in addition to the three episodes in the previous 6 months) were eligible to the study.

We excluded children with a history of severe exacerbations requiring systemic glucocorticoid, a chest infection or hospitalization for asthma or a treatment with inhaled glucocorticoids or methyl-xanthine during the previous 4 weeks or with oral glucocorticoid in the previous 8 weeks.

Children were stratified according to a 1 : 1 balanced ratio on the basis of the presence or absence of risk factors for developing persistent asthma (22), i.e., at least one of: (1) atopic dermatitis or eczema; (2) asthma in a first-degree relative; (3) eosinophilia >4% in a previous blood exam in the last 6 months.

Protocol

We randomly assigned patients to one of the three treatment groups for 12 weeks:

- (1) *Regular beclomethasone group*: beclomethasone (Clenil Aerosol [Chiesi Farmaceutici, Parma, Italy]) 400 µg/vial, one vial bid, plus salbutamol (Ventmax [Chiesi Farmaceutici]) 2500 µg/vial, one vial prn;
- (2) *Prn combination group (beclomethasone/salbutamol)*: placebo 1 vial bid, plus fixed combination of beclomethasone and salbutamol (Clenil Compositum [Chiesi Farmaceutici]), 800 µg beclomethasone + 1600 µg salbutamol/vial, one vial prn;

- (3) *Prn salbutamol group*: placebo one vial bid plus salbutamol 2500 µg/vial, one vial prn.

Treatments included only commercial preparations (blinded by the manufacturer) available for nebulization so that we could compare treatments available in clinical practice and to maintain the double-blind study design.

To reduce variability in drug delivery, all drugs were delivered with the same nebulizer (Clenny aerosol; Medel, Parma, Italy) using a tight-fitting face mask.

Parents/guardians were trained in the correct use of the nebulizer and instructed to keep daily records of their child's symptoms, recording scores for wheeze, cough, and shortness of breath on diary cards. Symptoms were recorded separately for daytime and night-time scores on the diary cards, using a four-point rating scale ranging from 0 (no symptoms) to 3 (disabling symptom) (8). Parents were also asked to record the number of occasions during the night that they were awakened because of the child's asthma symptoms, the number of occasions on which rescue medication was used for relief of symptoms, and the daily number of nebulizations for compliance assessment.

Parents were instructed to administer the prn medication only for symptom relief. The use any bronchodilator other than the study drugs was not allowed.

Clinic visits took place at the beginning (Visit 1) and end (Visit 2) of the run-in period and thereafter on study weeks 2, 4, 8, and 12. During each of these visits, the investigator verified compliance with assigned treatment by counting returned vials and reviewing diary cards. Compliant patients were considered to be those who had taken at least 75% of the scheduled doses of study medication by counting the returned unused vials and had filled out the diary cards consistently since their last visit.

Exacerbations were defined as episodes of progressive increase in shortness of breath, cough or wheezing (or some combination of these symptoms) that required a change in medication (8, 23). Only exacerbations confirmed by the study investigator were included in the analysis. Exacerbations were treated according to international guidelines (23). Morning salivary cortisol was measured in a subgroup of 91 patients who were equally distributed among the three groups (SALI-TUBES 100, SLV-4158).

Outcome measures

The primary outcome measure of the study was the percentage of symptom-free days during the 12-week study period. A symptom free day (as recorded on diary cards) was defined as a lack of wheezing, coughing, shortness of breath and patients/parents' nocturnal awakenings in 24 h. This definition did not include use, or lack of use, of relief medication.

Secondary outcomes included daily (24 h), daytime and night-time wheezing, coughing and shortness of breath score; number of nocturnal awakenings (children and parents); daily (24 h), daytime and night-time number of doses of relief medication; percentage of days without the need for relief medication; frequency and number of exacerbations and time to first exacerbation.

Statistical analysis

The sample size was calculated for superiority of treatment with regular beclomethasone or prn combination vs prn salbutamol. Based on previous data (8), we calculated that regular beclomethasone would increase the percentage of symptom-free days by 15% compared with prn salbutamol, with a standard deviation of 30%. At an alpha level of 0.05, beta 0.02, a sample of 240 patients in total

(96 in the regular beclomethasone group, 96 in the prn combination group, and 48 in the prn salbutamol group) was required. For primary variable, the three treatment groups were compared by using a nonparametric method (Wilcoxon sum rank test).

Other analyses were conducted on prespecified secondary end-points and performed as repeated comparisons between combinations of groups. Values of secondary efficacy variables recorded on the diary cards were averaged across each 2-week treatment period, summarized, and tested for normality. When they were found to be normal, they were analyzed within treatment groups by calculating, for each 2-week period, the 95% CI for the mean changes from baseline. Comparisons between groups were made using an analysis of covariance model for the mean values calculated in the last 2-week period, including terms for country, treatment and subgroup effects and baseline values as a covariate. The mean values of the 2-week run-in period were considered baseline values for parameters recorded on the diary cards.

In the event of a subject premature withdrawal from the study, the 'last observation carried forward' (LOCF) method was used to deal with missing data. The frequency of asthma exacerbations and the use of oral glucocorticoids were compared using chi-square test or two-tailed Fisher exact test. Kaplan–Meier estimates of survival times were used to compare the time to first exacerbation and the time to first exacerbation requiring oral glucocorticoids.

The number of patients experiencing adverse events or adverse drug reactions in the three groups was compared using chi-square test and two-tailed Fisher exact test, respectively. Statistical significance was declared when *P* values were ≤ 0.05 . The final analysis was conducted on an intention-to-treat basis.

Results

Subject characteristics

The three groups had similar baseline characteristics (Table 1). Of the 283 children recruited, 276 were random-

ized and 267 completed the 12-week study period (Fig. 1). Withdrawal rates after randomization were no different between groups (*P* = 0.456). Adherence to regular study medication regimens was no different between groups and satisfied the predefined level of $> 75\%$.

Primary outcome

As compared with prn salbutamol (61.0 ± 24.83 [SD]), the percentage of symptom-free days was significantly higher with regular beclomethasone (69.6 ± 20.89 ; *P* = 0.034) but not with prn combination (64.9 ± 24.74 ; Table 2).

A *post hoc* analysis of symptom-free days during the last month of treatment, i.e., when children symptomatic at baseline had become stable (Fig. 2), showed that the percentage of symptom-free days was significantly higher in both the regular beclomethasone and prn combination groups as compared with the prn salbutamol group (Table 2).

No difference was found in the primary outcome between children with or without risk factors for asthma (*P* > 0.05, all comparisons, data not shown).

Secondary outcomes

Symptoms. As expected, considering that children were recruited when symptomatic ($23.1 \pm 19.9\%$ symptom-free days during run-in), most symptom-related outcomes improved in all groups (Table 3; *P* < 0.05), particularly during the first 2 weeks of treatment and continuing until the end of Week 12 (Fig. 2). Exceptions were nocturnal awakenings and the number of uses of rescue medication,

Table 1. Baseline characteristics

	Regular beclomethasone (<i>n</i> = 110)	Prn combination (<i>n</i> = 110)	Prn salbutamol (<i>n</i> = 56)
Male, <i>n</i> (%)	64 (58.2)	68 (61.8)	34 (60.7)
Risk factors for asthma, <i>n</i> (%)	57 (51.8)	60 (54.5)	30 (53.6)
Age, year	2.35 $\pm$ 0.81	2.26 $\pm$ 0.79	2.29 $\pm$ 0.78
Weight, kg	15.4 $\pm$ 2.82	14.7 $\pm$ 2.57	14.9 $\pm$ 2.74
Height, cm	97.5 $\pm$ 9.19	95.5 $\pm$ 8.26	96.0 $\pm$ 9.61
Duration of wheezing, year	1.59 $\pm$ 0.87	1.53 $\pm$ 0.84	1.43 $\pm$ 0.82
Symptom-free days, %	21.4 $\pm$ 18.3	23.5 $\pm$ 19.1	25.9 $\pm$ 21.0
Daytime symptom score	1.47 $\pm$ 0.85	1.37 $\pm$ 0.82	1.23 $\pm$ 0.74
Night-time symptom score	1.01 $\pm$ 0.83	1.00 $\pm$ 0.93	1.00 $\pm$ 0.88
Daytime wheezing score	0.35 $\pm$ 0.36	0.30 $\pm$ 0.33	0.26 $\pm$ 0.31
Night-time wheezing score	0.26 $\pm$ 0.30	0.23 $\pm$ 0.34	0.21 $\pm$ 0.31
Daytime coughing score	0.87 $\pm$ 0.40	0.82 $\pm$ 0.40	0.75 $\pm$ 0.43
Night-time coughing score	0.56 $\pm$ 0.41	0.56 $\pm$ 0.41	0.59 $\pm$ 0.46
Daytime shortness of breath score	0.25 $\pm$ 0.35	0.25 $\pm$ 0.35	0.22 $\pm$ 0.32
Night-time shortness of breath score	0.19 $\pm$ 0.32	0.21 $\pm$ 0.35	0.20 $\pm$ 0.30
No. of nocturnal awakenings (children)	0.26 $\pm$ 0.24	0.32 $\pm$ 0.34	0.29 $\pm$ 0.31
No. of nocturnal awakenings (parents/guardians)	0.48 $\pm$ 0.40	0.49 $\pm$ 0.46	0.49 $\pm$ 0.46
Daytime rescue medication, no. of uses	0.35 $\pm$ 0.41	0.26 $\pm$ 0.29	0.25 $\pm$ 0.25
Night-time rescue medication, no. of uses	0.15 $\pm$ 0.17	0.16 $\pm$ 0.18	0.17 $\pm$ 0.19
Days (24 h) without use of rescue medication, %	66.9 $\pm$ 24.04	70.6 $\pm$ 22.82	70.1 $\pm$ 22.45
Morning salivary cortisol, μ g/100 ml	7.22 $\pm$ 8.21	8.37 $\pm$ 15.98	6.35 $\pm$ 3.12

Values are mean of the 2-week run-in period $\pm$ SD. Beclomethasone = beclomethasone dipropionate.

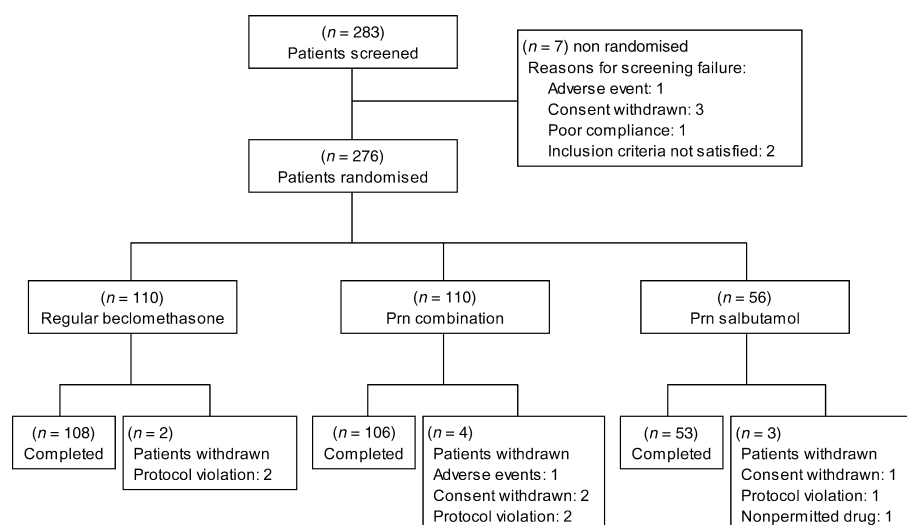


Figure 1. Patient flow.

in the prn salbutamol group. Both regular beclomethasone and prn combination were associated with fewer symptoms (daytime and night-time symptoms [Table 2], daytime and night-time coughing and daytime shortness of breath [data not shown]) and fewer nocturnal awakenings in both children and parents (Table 2), but not with lower wheezing and night-time shortness of breath scores (data not shown).

No difference was found in secondary outcomes between children with or without risk factors for asthma ($P > 0.05$, all comparisons, data not shown).

Exacerbations. Twenty-three exacerbations (14 of which required oral glucocorticoids) occurred during the study. Kaplan–Meier analysis showed that time to first exacerbation was longer in the regular beclomethasone group than in prn combination ($P = 0.03$) and prn salbutamol ($P = 0.03$) groups (Fig. 3). In addition, time to first exacerbation requiring oral glucocorticoids was longer in the regular beclomethasone group than in the prn salbutamol group ($P = 0.01$) but no different from the prn combination group ($P > 0.1$).

Intake of study drug and adverse events. Compared with the prn salbutamol group (56.3 ± 84.2 mg), the cumulative dose of salbutamol was lower in the prn combination group (30.1 ± 43.0 mg; $P < 0.001$) but not in the regular beclomethasone group (34.3 ± 42.3 mg; $P = 0.466$). Compared with regular beclomethasone (66.8 ± 6.8 mg), the cumulative dose of beclomethasone was lower in the prn combination group (15.1 ± 21.5 mg; $P = 0.032$).

The number of adverse events and of adverse drug reactions did not differ significantly between treatment groups ($P > 0.1$; Table 2).

Values of morning salivary cortisol did not change from baseline in any group (Table 3).

Discussion

This study shows that nebulized treatment with regular beclomethasone is superior to prn salbutamol alone in preschool children with frequent wheezing. Nebulized treatment with regular beclomethasone increases the percentage of symptom-free days (the primary outcome of the study) and improves several important secondary outcomes, including exacerbations (24). Prn combination was not statistically superior to prn salbutamol although not different from regular beclomethasone on the primary outcome. Prn combination was more effective than prn salbutamol on several secondary severity outcomes.

Although recommended by some international guidelines (7) regular treatment with inhaled glucocorticoids remains controversial (3, 25). In preschool children with wheeze, Bisgaard et al. showed that regular inhaled fluticasone was more effective than placebo in reducing respiratory symptoms and rescue medication use and in decreasing exacerbations, but the effect was considered to be too small to warrant continuous treatment (8). Guilbert et al. confirmed that regular inhaled glucocorticoids significantly increased the percentage of episode-free days and decreased the number of exacerbations in preschool children with wheeze, but they studied only children with risk factors for asthma (10). Similarly, Roorda et al. (26) and Chavasse et al. (27) found that preschool children with wheeze who had a family history of asthma responded to inhaled glucocorticoids with a decrease in symptoms. In contrast, other studies, albeit conducted mostly in even younger children, found no effect of treatment with regular glucocorticoids on respiratory symptoms (11, 28), regardless of whether children had risk factors for asthma (12).

Intermittent inhaled glucocorticoid therapy (2-week courses) has no effect on the progression from episodic to persistent wheezing and no short-term benefit during

Table 2. Comparisons between treatment groups

	Regular beclomethasone (<i>n</i> = 110)	Prn combination (<i>n</i> = 110)	Prn salbutamol (<i>n</i> = 56)	<i>P</i> values; [95% CI]*
Symptom-free days, Weeks 1–12, %, mean ± SD	69.6 ± 20.89	64.9 ± 24.74	61.0 ± 24.83	Regular beclomethasone vs prn salbutamol: <i>P</i> = 0.034; [0.58; 13.15] Regular beclomethasone vs prn combination: <i>P</i> = 0.293; [−2.38; 7.62] Prn combination vs prn salbutamol: <i>P</i> = 0.248; [−2.38; 10.71]
Symptom-free days, Weeks 9–12, %, mean ± SD	79.7 ± 23.11	77.4 ± 26.37	69.5 ± 28.66	Regular beclomethasone vs prn salbutamol: <i>P</i> = 0.016; [0; 16.01] Regular beclomethasone vs prn combination: <i>P</i> = 0.727; [−2.14; 3.57] Prn combination vs prn salbutamol: <i>P</i> = 0.033; [0; 14.29]
Daytime symptom score	0.32	0.32	0.55	Regular beclomethasone vs prn salbutamol: <i>P</i> = 0.045; [−0.45; −0.01] Regular beclomethasone vs prn combination: <i>P</i> = 0.928; [−0.17; 0.19] Prn combination vs prn salbutamol: <i>P</i> = 0.037; [−0.46; −0.01]
Night-time symptom score	0.23	0.19	0.43	Regular beclomethasone vs prn salbutamol: <i>P</i> = 0.039; [−0.39; −0.01] Regular beclomethasone vs prn combination: <i>P</i> = 0.626; [−0.12; 0.19] Prn combination vs prn salbutamol: <i>P</i> = 0.014; [−0.43; −0.05]
No. of nocturnal awakenings (children)	0.05	0.05	0.17	Regular beclomethasone vs prn salbutamol: <i>P</i> < 0.001; [−0.19; −0.05] Regular beclomethasone vs. prn combination: <i>P</i> = 0.939; [−0.06; 0.05] Prn combination vs prn salbutamol: <i>P</i> < 0.001; [−0.18; −0.05]
No. of nocturnal awakenings (parents/guardians)	0.11	0.11	0.22	Regular beclomethasone vs prn salbutamol: <i>P</i> = 0.020; [−0.21; −0.02] Regular beclomethasone vs prn combination: <i>P</i> = 0.957; [−0.08; 0.08] Prn combination vs prn salbutamol: <i>P</i> = 0.018; [−0.21; −0.02]
Daytime rescue medication, no. of uses	0.09	0.09	0.16	Regular beclomethasone vs prn salbutamol: <i>P</i> = 0.156; [−0.18; 0.03] Regular beclomethasone vs prn combination: <i>P</i> = 0.995; [−0.08; 0.09] Prn combination vs prn salbutamol: <i>P</i> = 0.151; [−0.18; 0.03]
Night-time rescue medication, no. of uses	0.04	0.04	0.08	Regular beclomethasone vs prn salbutamol: <i>P</i> = 0.095; [−0.09; 0.01] Regular beclomethasone vs prn combination: <i>P</i> = 0.909; [−0.04; 0.04] Prn combination vs prn salbutamol: <i>P</i> = 0.077; [−0.09; 0.00]
Patients with adverse events, <i>n</i> (%)	22 (20%)	30 (27.3%)	17 (30.4%)	Regular beclomethasone vs prn salbutamol: <i>P</i> = 0.137; [NA] Regular beclomethasone vs prn combination: <i>P</i> = 0.204; [NA] Prn combination vs prn salbutamol: <i>P</i> = 0.677; [NA]
Patients with drug related adverse events, <i>n</i> (%)	2 (1.8%)	4 (3.6%)	3 (5.4%)	Regular beclomethasone vs prn salbutamol: <i>P</i> = 0.337; [NA] Regular beclomethasone vs prn combination: <i>P</i> = 0.683; [NA] Prn combination vs prn salbutamol: <i>P</i> = 0.689; [NA]
Patients with serious adverse events, <i>n</i> (%)	0 (0%)	0 (0%)	1 (1.8%)	Regular beclomethasone vs prn salbutamol: <i>P</i> = 0.337 [NA] Regular beclomethasone vs prn combination: <i>P</i> = NA; [NA] Prn combination vs prn salbutamol: <i>P</i> = 0.337; [NA]

Values are adjusted means of the last 2-week period. NA, not assessable, Beclomethasone, beclomethasone dipropionate; CI, confidence interval.

*CI for primary variable were calculated *post hoc* through the Hodges-Lehmann's method

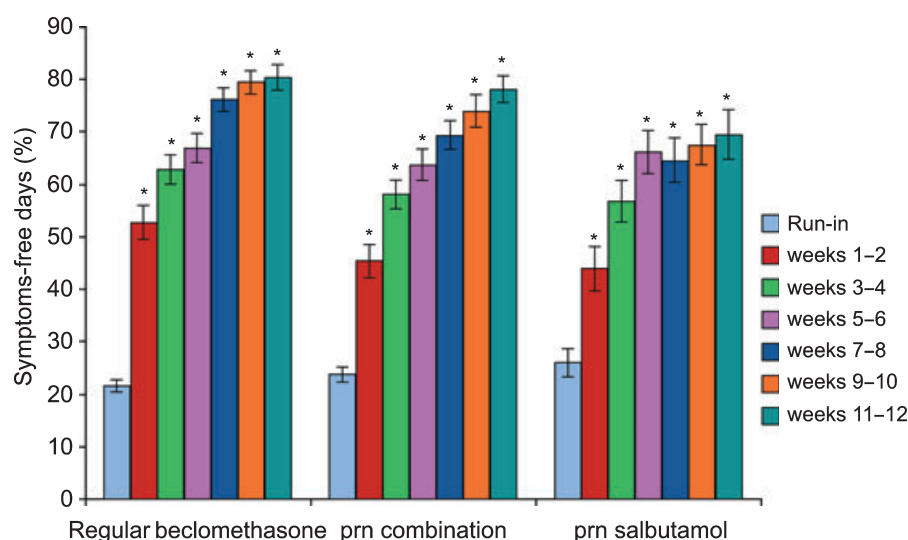


Figure 2. Symptoms-free days. Percentage of symptoms-free days over 2 weeks during run-in and the 12-week study period with one of the following: (i) twice-daily inhaled beclomethasone and prn salbutamol (regular beclomethasone); (ii) twice-daily inhaled placebo and prn inhaled beclomethasone/salbutamol (prn combination); (iii) twice-daily inhaled placebo and prn inhaled salbutamol (prn salbutamol). Data are mean $\pm$ SE. * $P < 0.001$ vs run in.

episodes of wheezing in the first 3 years of life (13). The episodic use (7-day courses) of a nebulized glucocorticoid or an oral leukotriene receptor antagonist does not increase the number of episode-free days (primary outcome parameter) but improves symptom severity (14, 29). The effects are more pronounced in children with risk factors for developing persistent asthma (14, 29). Similarly high-dose fluticasone administered at the onset of an upper respiratory infection and continued for

a maximum of 10 days reduce the use of rescue oral glucocorticoids, but the effect is associated with reduced gain in height and weight (15).

Our study confirms the results of some of these previous studies (8, 10, 26, 27, 30) on the benefit of regular treatment with inhaled glucocorticoids in preschool children with frequent wheezing, irrespective of risk factors for asthma. In fact, subgroup comparisons in our study, for both primary and secondary outcomes,

Table 3. Mean changes vs baseline

	Regular beclomethasone (<i>n</i> = 110)	<i>P</i> -values [95% CI]	Prn combination (<i>n</i> = 110)	<i>P</i> -values [95% CI]	Prn salbutamol (<i>n</i> = 56)	<i>P</i> -values [95% CI]
Symptom-free days	58.84 $\pm$ 29.41	$P < 0.001$ [53.28; 64.40]	54.37 $\pm$ 30.12	$P < 0.001$ [48.68; 60.06]	43.34 $\pm$ 43.11	$P < 0.001$ [31.79; 54.88]
Daytime symptom score	-1.11 $\pm$ 0.90	$P < 0.001$ [-1.28; -0.94]	-1.03 $\pm$ 0.92	$P < 0.001$ [-1.21; -0.86]	-0.69 $\pm$ 1.04	$P < 0.001$ [-0.97; -0.41]
Night-time symptom score	-0.77 $\pm$ 0.88	$P < 0.001$ [-0.93; -0.60]	-0.80 $\pm$ 0.92	$P < 0.001$ [-0.97; -0.63]	-0.56 $\pm$ 0.99	$P < 0.001$ [-0.82; -0.29]
Daytime wheezing score	-0.29 $\pm$ 0.36	$P < 0.001$ [-0.36; -0.22]	-0.24 $\pm$ 0.31	$P < 0.001$ [-0.29; -0.18]	-0.18 $\pm$ 0.32	$P < 0.001$ [-0.26; -0.09]
Night-time wheezing score	-0.21 $\pm$ 0.30	$P < 0.001$ [-0.27; -0.16]	-0.18 $\pm$ 0.35	$P < 0.001$ [-0.25; -0.12]	-0.14 $\pm$ 0.31	$P = 0.001$ [-0.22; -0.06]
Daytime coughing score	-0.64 $\pm$ 0.51	$P < 0.001$ [-0.74; -0.55]	-0.59 $\pm$ 0.51	$P < 0.001$ [-0.69; -0.50]	-0.39 $\pm$ 0.61	$P < 0.001$ [-0.55; -0.23]
Night-time coughing score	-0.42 $\pm$ 0.49	$P < 0.001$ [-0.51; -0.33]	-0.44 $\pm$ 0.39	$P < 0.001$ [-0.51; -0.36]	-0.30 $\pm$ 0.59	$P < 0.001$ [-0.46; -0.14]
Daytime shortness of breath score	-0.18 $\pm$ 0.32	$P < 0.001$ [-0.24; -0.12]	-0.20 $\pm$ 0.35	$P < 0.001$ [-0.27; -0.14]	-0.12 $\pm$ 0.39	$P = 0.026$ [-0.22; -0.01]
Night-time shortness of breath score	-0.13 $\pm$ 0.30	$P < 0.001$ [-0.19; -0.08]	-0.18 $\pm$ 0.34	$P < 0.001$ [-0.24; -0.12]	-0.12 $\pm$ 0.32	$P = 0.009$ [-0.20; -0.03]
No. of nocturnal awakenings (children)	-0.20 $\pm$ 0.24	$P < 0.001$ [-0.25; -0.15]	-0.25 $\pm$ 0.33	$P < 0.001$ [-0.31; -0.18]	-0.10 $\pm$ 0.39	$P = 0.062$ [-0.21; 0.01]
No. of nocturnal awakenings (parents/guardians)	-0.36 $\pm$ 0.44	$P < 0.001$ [-0.44; -0.28]	-0.38 $\pm$ 0.45	$P < 0.001$ [-0.46; -0.29]	-0.26 $\pm$ 0.50	$P < 0.001$ [-0.39; -0.13]
Daytime rescue medication, no. of uses	-0.24 $\pm$ 0.44	$P < 0.001$ [-0.32; -0.16]	-0.17 $\pm$ 0.38	$P < 0.001$ [-0.24; -0.10]	-0.09 $\pm$ 0.42	$P = 0.113$ [-0.20; 0.02]
Night-time rescue medication, no. of uses	-0.10 $\pm$ 0.21	$P < 0.001$ [-0.14; -0.06]	-0.12 $\pm$ 0.20	$P < 0.001$ [-0.16; -0.08]	-0.08 $\pm$ 0.25	$P = 0.022$ [-0.15; -0.01]
Salivary cortisol, μ g/100 ml	-1.92 $\pm$ 7.39	$P = 0.123$ [-4.38; 0.55]	0.60 $\pm$ 27.18	$P = 0.897$ [-8.74; 9.94]	0.55 $\pm$ 3.20	$P = 0.466$ [-1.00; 2.09]

Values are mean $\pm$ SD change from baseline (mean of the 2-week run-in period) to the end of the treatment period (mean values of Weeks 11–12). Beclomethasone, beclomethasone dipropionate; CI, confidence interval.

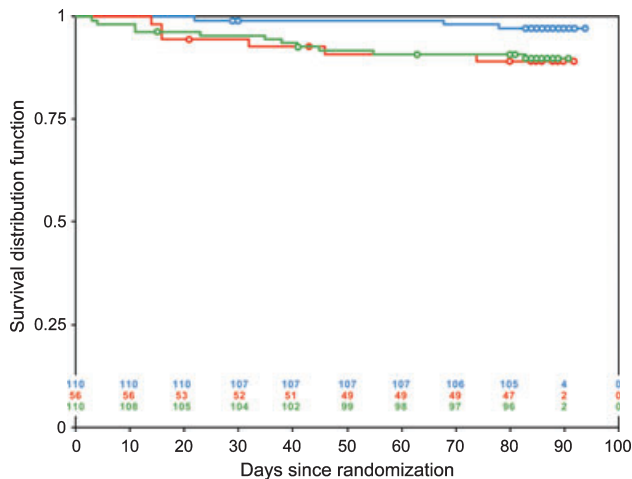


Figure 3. Kaplan–Meier estimates of the time to first asthma exacerbation in the intention-to-treat population. Blue line regular beclomethasone group; green line prn combination group; red line prn salbutamol group. $P = 0.03$ for regular beclomethasone vs prn combination and vs prn salbutamol; $P = 0.88$ for prn combination vs prn salbutamol; circles are censored treatment, colored numbers are numbers at risk in each group.

showed no difference between children with or without risk factors for developing asthma.

The 8.6% increase in symptom-free days with regular use of inhaled glucocorticoids detected in our study was statistically significant but small, similar to the 4.8–7.4% difference between glucocorticoids and placebo treatments previously reported in similar populations (10, 31). However, in our and others' studies, the improvement in number of symptom-free days was associated with improvement in several important secondary outcomes, such as exacerbations, nocturnal awakenings, and symptom scores, possibly making the overall effect clinically relevant. The clinical relevance of the regular use of inhaled glucocorticoids needs to be critically weighed against their potential systemic side effects (32), particularly in the light of the fact they have no effect on the natural course of the disease (10, 13, 18).

This is one of the reasons we investigated in this age group of children the effect of the prn beclomethasone/salbutamol combination: a treatment modality recently shown to be effective in adults with mild asthma (21), but never tested in children. Although we found that the effect of prn combination on symptom-free days or on exacerbations was not statistically different from that of salbutamol alone, prn combination was more effective than prn salbutamol on other relevant secondary outcomes (e.g., nocturnal awakenings) and not different from regular beclomethasone in almost all secondary outcomes. Also, a *post hoc* analysis of symptom-free days measured during the last 4 weeks of treatment (i.e., when children symptomatic at baseline had become stable),

showed a statistically significant increase in symptom-free days with prn combination as compared with salbutamol alone, suggesting its protective effect when given in stable conditions (21). Combination treatment in our study was associated with a lower cumulative dose of salbutamol and of glucocorticoid. Even if the real sparing effect of this prn combination cannot be established in this study, as we did not titrate the dose of inhaled glucocorticoid and used a lower dose of salbutamol in the combination, we believe that our findings are of interest. In fact, because (a) discontinuation rates of regular asthma medications are very high in preschool children (33), (b) the common overreliance on bronchodilators alone is associated with increased morbidity and mortality in children (34), and (c) the overall effect of regular inhaled glucocorticoids is modest, we suggest that prn combination should be considered and further investigated as a treatment option. Indeed there is increasing evidence that glucocorticoids have a relatively rapid suppressive effect on inflammation and that prn combination treatment could be easier than a fixed daily anti-inflammatory regimen, thus encouraging adherence (35).

While guidelines recommend use of a compressor-driven nebulizer with face mask as a second choice after pressurized metered-dose inhaler plus dedicated spacer with face mask for preschool children (6, 36), nebulizers are frequently used in clinical practice to overcome problems with inhaler technique (37–39). In children aged 1–5 years nebulizers are still the most frequently used devices in the United States (81%) and southern Europe (67%) (40), and nebulized glucocorticoids have been shown to be effective (9). Very young children may lack the ability to use metered-dose inhalers correctly (41), and no clinically relevant difference has been shown between hand-held inhalers and nebulizers (37, 42).

In our study regular glucocorticoid treatment and prn combination were compared with different doses of beclomethasone and salbutamol. This limitation had to be accepted from the beginning because of the formulations commercially available. The aim of the study was mainly a proof-of-concept, i.e., to explore whether the prn inhaled combination of a glucocorticoid and a short-acting bronchodilator is more effective than the short-acting bronchodilator alone. Thus, any combination dose would have been arbitrary. In fact, in similar proof-of-concept studies conducted in adults (43–45), not only different doses of drugs were used, but also different prn drugs [e.g., terbutaline vs formoterol vs budesonide/formoterol combination in Rabe et al. (44)]; nonetheless, those studies provided clinically relevant information.

It could be also argued that a longer study period might have allowed us to detect a higher number of exacerbations. For the primary outcome (symptom-free days), a duration of 12 weeks was previously adopted in similar studies (8, 26, 46); and we showed comparable results to those of even longer trials (10, 31).

Our study shows that regular treatment with nebulized glucocorticoids is the most effective treatment for preschool children with frequent wheeze regardless of the presence or absence of risk factors for developing asthma. Moreover, as a proof-of-concept study, these results suggest that the rescue use of a fixed combination of a short-acting bronchodilator and an inhaled glucocorticoid could be an alternative to a prn short-acting bronchodilator alone; this deserves to be further evaluated.

Sources of funding

The study was funded by Chiesi Farmaceutici SpA, Parma, Italy. The sponsor of the study was involved with the study design. The sponsor had no role in data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all

the data in the study and had final responsibility for the decision to submit for publication.

Acknowledgments

Investigators of the BEST for CHILDREN study group were: Dr Henryk Mazurek, Dr Marcin Wronski, Dr Jolanta Pietraszek-Mamcarz, Dr Agata Swierczek, Dr Jadwiga Kaczmarek and Prof. Jerzy Hofman from Poland; Prof. Olga Illarionovna Lasysya, Prof. Aryayev Nikolay Leonidovich, Prof. Viktoria Pavlovna Kostromina, Prof. Senatorova Anna Sergeyivna, Prof. Kobets Tatyana Vladimirovna, Prof. Antypkin Yuriy Genadievich, Prof. Lapshyn Vladimir Fedorovich, Dr Tatyana Ivanovna Okul, Prof. Svetlana Alexeevna Mokia-Serbina, Prof. Ekaterina Dmitrievna Duka, Prof. Leonid Sergeevich Ovcharenko, Prof. Tatyana Alexandrovna Kryuchko and Prof. Lyudmila Vladimirovna Vashchenko from Ukraine. We are indebted to E. Veratelli for her scientific secretarial assistance.

References

- Kuehni CE, Strippoli MP, Low N, Brooke AM, Silverman M. Wheeze and asthma prevalence and related health-service use in white and south Asian preschoolchildren in the United Kingdom. *Clin Exp Allergy* 2007;**37**:1738–1746.
- Saglani S, Wilson N, Bush A. Should preschool wheezers ever be treated with inhaled corticosteroids? *Semin Respir Crit Care Med* 2007;**28**:272–285.
- Brand PL, Baraldi E, Bisgaard H, Boner AL, Castro-Rodriguez JA, Custovic A et al. Definition, assessment and treatment of wheezing disorders in preschool children: an evidence-based approach. *Eur Respir J* 2008;**32**:1096–1110.
- Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med* 1995;**332**:133–138.
- Kaditis AG, Winnie G, Syrogiannopoulos GA. Anti-inflammatory pharmacotherapy for wheezing in preschool children. *Pediatr Pulmonol* 2007;**42**:407–420.
- National Heart, Lung, and Blood Institute. National Asthma Education and Prevention Program. Expert Panel Report 3. Guidelines for the Diagnosis and Management of Asthma, 2007. Publication No. 07-4051.
- Global Strategy for the Diagnosis and Management of Asthma in Children 5 Years and Younger, Global Initiative for Asthma (GINA) 2009. Available from: <http://www.ginasthma.org>.
- Bisgaard H, Gillies J, Groenewald M, Maden C. The effect of inhaled fluticasone propionate in the treatment of young asthmatic children: a dose comparison study. *Am J Respir Crit Care Med* 1999;**160**:126–131.
- de Blic J, Delacourt C, Le Bourgeois M, Mahut B, Ostinelli J, Caswell C et al. Efficacy of nebulized budesonide in treatment of severe infantile asthma: a double-blind study. *J Allergy Clin Immunol* 1996;**98**:14–20.
- Guilbert TW, Morgan WJ, Zeiger RS, Mauger DT, Boehmer SJ, Szeffler SJ et al. Long-term inhaled corticosteroids in preschool children at high risk for asthma. *N Engl J Med* 2006;**354**:1985–1997.
- Barrueto L, Mallol J, Figueroa L. Beclomethasone dipropionate and salbutamol by metered dose inhaler in infants and small children with recurrent wheezing. *Pediatr Pulmonol* 2002;**34**:52–57.
- Hofhuis W, van der Wiel EC, Nieuwhof EM, Hop WC, Affourtit MJ, Smit FJ et al. Efficacy of fluticasone propionate on lung function and symptoms in wheezy infants. *Am J Respir Crit Care Med* 2005;**171**:328–333.
- Bisgaard H, Hermansen MN, Loland L, Halkjaer LB, Buchvald F. Intermittent inhaled corticosteroids in infants with episodic wheezing. *N Engl J Med* 2006;**354**:1998–2005.
- Bacharier LB, Phillips BR, Zeiger RS, Szeffler SJ, Martinez FD, Lemanske RF Jr et al. Episodic use of an inhaled corticosteroid or leukotriene receptor antagonist in preschool children with moderate-to-severe intermittent wheezing. *J Allergy Clin Immunol* 2008;**122**:1127–1135. e8.
- Ducharme FM, Lemire C, Noya FJ, Davis GM, Alos N, Leblond H et al. Preemptive use of high-dose fluticasone for virus-induced wheezing in young children. *N Engl J Med* 2009;**360**:339–353.
- Panickar J, Lakhnapaul M, Lambert PC, Kenia P, Stephenson T, Smyth A et al. Oral prednisolone for preschool children with acute virus-induced wheezing. *N Engl J Med* 2009;**360**:329–338.
- Frey U, von Mutius E. The challenge of managing wheezing in infants. *N Engl J Med* 2009;**360**:2130–2133.
- Murray CS, Woodcock A, Langley SJ, Morris J, Custovic A. Secondary prevention of asthma by the use of inhaled fluticasone propionate in Wheezy Infants (IFWIN): double-blind, randomised, controlled study. *Lancet* 2006;**368**:754–762.
- Chavasse RJ, Bastian-Lee Y, Seddon P. How do we treat wheezing infants? Evidence or anecdote. *Arch Dis Child* 2002;**87**:546–547.
- Vermeire PA, Rabe KF, Soriano JB, Maier WC. Asthma control and differences in management practices across seven European countries. *Respir Med* 2002;**96**:142–149.

21. Papi A, Canonica GW, Maestrelli P, Paggiaro P, Olivieri D, Pozzi E et al. Rescue use of beclomethasone and albuterol in a single inhaler for mild asthma. *N Engl J Med* 2007;**356**: 2040–2052.
22. Castro-Rodriguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med* 2000;**162**: 1403–1406.
23. GINA. Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA). Available from: <http://www.ginasthma.org>, 2002.
24. Bisgaard H, Allen D, Milanowski J, Kalev I, Willits L, Davies P. Twelve-month safety and efficacy of inhaled fluticasone propionate in children aged 1 to 3 years with recurrent wheezing. *Pediatrics* 2004;**113**: e87–e94.
25. Castro-Rodriguez JA, Rodrigo GJ. Efficacy of inhaled corticosteroids in infants and preschoolers with recurrent wheezing and asthma: a systematic review with meta-analysis. *Pediatrics* 2009;**123**:e519–e525.
26. Roorda RJ, Mezei G, Bisgaard H, Maden C. Response of preschool children with asthma symptoms to fluticasone propionate. *J Allergy Clin Immunol* 2001;**108**:540–546.
27. Chavasse RJ, Bastian-Lee Y, Richter H, Hilliard T, Seddon P. Persistent wheezing in infants with an atopic tendency responds to inhaled fluticasone. *Arch Dis Child* 2001;**85**: 143–148.
28. Van Bever HP, Schuddincx L, Wojciechowski M, Stevens WJ. Aerosolized budesonide in asthmatic infants: a double blind study. *Pediatr Pulmonol* 1990;**9**:177–180.
29. Becker AB. Asthma in the preschool child: still a rose by any other name? *J Allergy Clin Immunol* 2008;**122**: 1136–1137.
30. Bisgaard H, Munck SL, Nielsen JP, Petersen W, Ohlsson SV. Inhaled budesonide for treatment of recurrent wheezing in early childhood. *Lancet* 1990;**336**:649–651.
31. Teper AM, Kofman CD, Szulman GA, Vidaurreta SM, Maffey AF. Fluticasone improves pulmonary function in children under 2 years old with risk factors for asthma. *Am J Respir Crit Care Med* 2005;**171**:587–590.
32. Pedersen S. Clinical safety of inhaled corticosteroids for asthma in children: an update of long-term trials. *Drug Saf* 2006;**29**:599–612.
33. Zuidgeest MG, Smit HA, Bracke M, Wijga AH, Brunekreef B, Hoekstra MO et al. Persistence of asthma medication use in preschool children. *Respir Med* 2008;**102**:1446–1451.
34. Butz AM, Tsoukleris M, Donithan M, Hsu VD, Mudd K, Zuckerman IH et al. Patterns of inhaled antiinflammatory medication use in young underserved children with asthma. *Pediatrics* 2006;**118**:2504–2513.
35. Barnes PJ. Scientific rationale for using a single inhaler for asthma control. *Eur Respir J* 2007;**29**:587–595.
36. Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA). Available from: <http://www.ginasthma.org>, 2007.
37. Boe J, Dennis JH, O'Driscoll BR, Bauer TT, Carone M, Dautzenberg B et al. European Respiratory Society Guidelines on the use of nebulizers. *Eur Respir J* 2001;**18**:228–242.
38. Mason N, Roberts N, Yard N, Partridge MR. Nebulisers or spacers for the administration of bronchodilators to those with asthma attending emergency departments? *Respir Med* 2008;**102**: 993–998.
39. Szefer SJ, Baker JW, Uryniak T, Goldman M, Silkoff PE. Comparative study of budesonide inhalation suspension and montelukast in young children with mild persistent asthma. *J Allergy Clin Immunol* 2007;**120**: 1043–1050.
40. Bisgaard H, Szefer S. Prevalence of asthma-like symptoms in young children. *Pediatr Pulmonol* 2007;**42**: 723–728.
41. Dolovich MB, Ahrens RC, Hess DR, Anderson P, Dhand R, Rau JL et al. Device selection and outcomes of aerosol therapy: evidence-based guidelines: American College of Chest Physicians/American College of Asthma, Allergy, and Immunology. *Chest* 2005;**127**: 335–371.
42. Bisca N, Cernatescu I, Dragomir D, Iacomi A, Mirceanu M, Orascanu D. Comparison of the efficacy and safety of beclomethasone dipropionate suspension for nebulization and beclomethasone dipropionate via a metered-dose inhaler in paediatric patients with moderate to severe exacerbation of asthma. *Respir Med* 2003;**97**: S15–S20.
43. O'Byrne PM, Bisgaard H, Godard PP, Pistolesi M, Palmqvist M, Zhu Y et al. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. *Am J Respir Crit Care Med* 2005;**171**:129–136.
44. Rabe KF, Atienza T, Magyar P, Larsson P, Jorup C, Lalloo UG. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study. *Lancet* 2006;**368**: 744–753.
45. Rabe KF, Pizzichini E, Stallberg B, Romero S, Balanzat AM, Atienza T et al. Budesonide/formoterol in a single inhaler for maintenance and relief in mild-to-moderate asthma: a randomized, double-blind trial. *Chest* 2006;**129**:246–256.
46. Carlsen KC, Stick S, Kamin W, Cirule I, Hughes S, Wixon C. The efficacy and safety of fluticasone propionate in very young children with persistent asthma symptoms. *Respir Med* 2005;**99**: 1393–1402.