Once versus twice daily budesonide metered-dose inhaler in children with mild to moderate asthma: effect on symptoms and bronchial responsiveness

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ABSTRACT

Background: Simplifying dosing regimens could improve both adherence and asthma-related morbidity. However, there is little information on the effectiveness of once-daily budesonide, administered through a metered dose inhaler (MDI) plus spacer, on asthma symptoms and pulmonary function in asthmatic children.

Methods: The aim of this study was to compare the effect of once-daily versus twice-daily doses of inhaled budesonide on symptoms, lung function and bronchial hyperresponsiveness (BHR) in asthmatic children. This study was a randomized, single-blind, parallel clinical trial. Patients received budesonide from an MDI either 800 µg as a daily dose or fractionated in 400 µg twice a day for 12 weeks. Statistical analysis was performed using tests for independent and paired samples.

Results: In both groups, asthma symptoms significantly decreased. However, the improvement in asthma symptoms, decrease in BHR and treatment adherence were significantly greater in the once-daily group than in the twice-daily group (p < 0.05). No significant differences were found between the two groups in spirometric parameters, morning peak expiratory flow or plasma cortisol values.

Conclusions: Once-daily administration of 800 µg of inhaled budesonide administered by MDI plus spacer was more effective in controlling symptoms and improving BHR than fractionating the dose to 400 µg twice daily. The differences observed in this study could have been due to the greater adherence to treatment in patients in the once-daily group.

Key words: Inhaled corticosteroids. Asthma in children. Budesonide once-daily. Wheezing.

INTRODUCTION

At present, inhaled corticosteroids (ICS) are the first line medications for the treatment of asthma at all ages. However, even when ICS are very effective to control the disease, they need to be used as a long-term therapy where many aspects, mainly dependent on patients and treatments, are crucial to get the best possible clinical and functional benefits with minimal side effects, particularly in children. To achieve this goal simplified dosing regimens (e.g., once-daily administration) including good quality aerosols, good inhaler technique, close follow up of patients, and education of parents and patients on...
the importance of treatment adherence, are very impor-
tant for the treatment effectiveness\textsuperscript{15,16}. It has been reported that inhaling budesonide from
dry powder inhalers (DPI) once daily is as effective as
twice daily to control asthma in children and this may be an important advantage for parents and chil-
dren in terms of cost, comfort and adherence to treat-
ment\textsuperscript{12,14}. In addition, long-term treatment with budes-
onide once daily (200 or 400 \textmu g) has been found to be
safe and well tolerated in children and adults with
newly detected mild persistent asthma\textsuperscript{11,12}. Although there is a considerable body of informa-
tion on once daily administration of budesonide DPI
in children, little is known onto whether this effect-
iveness to control the disease can also be achieved by
administering generic budesonide through MDI plus
spacers in children. The latter would represent a
cost-effective alternative, particularly in developing
countries where DPI devices are still much more ex-
pensive than MDI and also may allow administering
inhaled corticosteroids to patients unable to use DPI.

The present study was undertaken to determine the
effect of once or twice daily administration of
generic budesonide MDI plus spacer on asthma
symptoms, spirometric lung function and airway re-
sponsiveness to methacholine, in children with
mild-moderate stable asthma.

METHODS

Subjects

Fifty atopic asthmatic children (32 boys, 18 girls),
with a mean age of 11 years (range 7-16 years), from
a low income population and that were looked after
at our Department of Pediatric Respiratory Medicine,
Hospital El Pino, Santiago, Chile, were invited to par-
ticipate in this study. They had mild to moderate per-
sisting asthma, without exacerbations in the last
4 months, no history of acute respiratory infection in
the last 4 weeks previous to randomization, and no
systemic steroids in the last four months. All of them
were on treatment with regular inhaled steroids up to
800 microgram daily of MDI beclomethasone dipro-
pionate (or equivalent) and on-demand inhaled salbu-
tamol, both delivered through a plastic opened spacer.

Study Design

This study was a randomized, single blind, two-
groups, parallel, and 12-week clinical trial. During a
four-week run in period children and mothers were
trained on inhalation technique, forced vital capacity
maneuvers and symptom recording (mainly wheez-
ing and cough). At the end of the run in, children
were randomly allocated into two study groups. One
group inhaled budesonide MDI, 400 mcg bid and the
other inhaled budesonide MDI, 800 mcg once a day
in the morning. Salbutamol on demand was used for
the relief of acute symptoms in both groups. MDI
aerosols were inhaled by mouth using a large plastic
spacer without valves. Instructions were given to
mothers on cleaning the device with detergent to de-
crease electrostatic charge. The inhalation technique
employed for all aerosols (budesonide and salbuta-
mol) was as follows. After shaking canister, MDI
aerosols were actuated into the spacer and slowly in-
haled by mouth from residual volume to total lung ca-
pacity, holding breath for 10 seconds and then breath
out slowly. Patients were instructed to rinse their
mouth with water after inhaling budesonide.

Clinical assessment

Children were scheduled to visit our clinic every
30 days in a period of 12 weeks. At each visit, com-
plete physical examination was done and parent-re-
ported asthma symptoms (wheezing, on a yes or no
bases) in the last 2 weeks before each visit were reg-
istered and employed for analysis.

Pulmonary function testing

Spirometric measurements were performed at en-
try (baseline) and at the end of the study using a heat-
ed pneumotachograph (model 3810, Hans Rudolph
Inc., USA) with the Medgraphics CPF-S processing
system (Medical Graphics Corp., MN., USA). Baseline
values for FVC, FEV\textsubscript{1}, FEF\textsubscript{25-75}, and FEV\textsubscript{1}/FVC were
obtained prior to methacholine challenge, during each
test day. Forced capacity maneuvers were done in
tricipate and best spirometric values were selected
according to ATS criteria for acceptability and repro-
ducibility\textsuperscript{13}. Short-acting beta 2 adrenergic agonists
were stopped 12 hours prior to lung function testing
and inhaled steroids were allowed as prescribed by
study physicians. None of the patients was on long
acting adrenergic agonists, oral steroids, antihista-
mics, or theophylline.

Methacholine challenge test was carried out if
patient’s FEV\textsubscript{1} is equal or above 80 % of predicted
value\textsuperscript{14} and according to a modified tidal breathing
method\textsuperscript{15,16}. Subjects performed all maneuvers in the
standing position and using nasal clip. Methacholine
chloride (ICN Biomedicals Inc., Ohio, USA) solutions
in normal saline were stored at 4° centigrade and neb-
ing 2 min. FEV
8 mg/ml were inhaled by quiet mouth breathing dur-
concentrations of methacholine from 0.03 mg/ml to
of air at a pressure of 344 kPa (50 psi.) and flow
Methacholine aerosol was delivered through a mouth
tube with volume extension piece.
Following inhalation of normal saline, doubling con-
centrations of methacholine were logarithmically trans-
then given by a large volume valved spacer.

Adherence to treatment
Adherence to treatment was estimated from par-
ents and children reports and also from canister
weight. All MDI canisters provided to children in both
groups were weighted before and when collected at
each corresponding visits to measure adherence to
treatment (medication canister weight).

Morning plasma cortisol
Fasten blood samples for plasmatic morning corti-
sol (between 8:00 and 9:30 hr AM) were obtained for
all patients at the beginning (randomization) and at
the end of the study; plasma cortisol was determined
employing radio-immunoassay considering as normal
values those ranging from 5 to 25 µg/dl.

Data analysis
The presence or absence of asthma symptoms at
every visit (yes or no) as reported by par-
ents was computed as a categorized clinical score for
comparison between entry and discharge. Concen-
trations of methacholine were logarithmically trans-
formed prior to all calculations and PC20 was then cal-
culated by linear interpolation of the final two points
by means of a computer program. The number of
double log-concentrations was then calculated (by
subtracting the initial logPC20 to final logPC20 and di-
viding the result by log2) and employed to assess the
change occurred in bronchial responsiveness to
methacholine and expressing it as doubling dose
change in PC20; one or more DD change in PC20
methacholine was considered as significant for the
purpose of the study17. An increase of 1 DD of the
trigger after treatment with inhaled corticosteroids
meant that double the amount of the trigger was
needed to achieve the same fall in FEV1.
Analysis of variance (ANOVA), parametric and non-
parametric test for paired and independent samples
used where appropriate for statistical analysis. The
limit of statistical significance was set at p < 0.05
(two tailed) and results are expressed as mean and
95 % confidence interval (95 % CI).
The study was undertaken with the permission of
the Hospital’s Ethics Committee and full informed,
written and signed consent were obtained from all
parents.

RESULTS
Of the 50 children initially enrolled, 44 completed
the study. Six children were withdrawn, three in each
group, and the main reasons were unwilling to con-
tinue with the study and failure to attend one or more
of the scheduled visits (methacholine challenge test).
There were not significant differences between
groups in height and weight; demographic, lung func-
tion and other characteristics of patients are sum-
marized in table I.
At the end of the study there was a significant clin-
cical improvement in both groups. However, the pro-
portion of children that still had asthma symptoms at
week 12 was significantly lower in the group that in-
haled budesonide once a day compared with the
group inhaling twice a day, (chi-square 4.29, p = 0.038)
(fig. 1).
The general measured adherence (by canister
weight) was significantly lower for the group of chil-
dren that inhaled budesonide twice daily (62.9 %;
95 %CI 54.5-71.3) as compared with those who in-
haled once daily (74.4 %; 95 %CI 68.9-79.9 %). In
both groups parents and children reported adherence
to treatment over 85 %, however, the agreement be-
tween reported and calculated was poor (kappa = 0.13)
(fig. 2).
There was not significant difference in mean
methacholine PC20 between entry and discharge for
any of the study groups. Although the group of chil-
dren that inhaled budesonide once daily showed an
increase in mean PC20 from 0.68 mg/mL to 1.48
mg/mL. It did not reach statistical significance.
However, when expressed as log PC20 doubling
dose change there was a significant improvement
(1 or more DD) in the once-daily group (1,22; 95 %CI,
0,60-1,85) as compared with the group that inhaled

Morning plasma cortisol was not significantly different between and within groups at entry or end of the study. There were no complications related with employed medications reported by patients or their mothers during the study.

DISCUSSION

This study shows that both, MDI budesonide given once (800 μg), or twice daily (400 μg BID) used for 16 weeks, are similarly effective to control asthma symptoms in children with mild to moderate asthma. However, once daily budesonide had a significant effect on improving BHR and was more effective in controlling asthma symptoms than administering the medication twice daily. The latter may be associated to the significantly higher adherence to treatment observed in the group of children who inhaled budesonide once daily.

These findings have been reported in the past using inhaled corticosteroids mainly administered by DPI in children and adults. In a randomized, double-blind, placebo-controlled, multicenter study which

### Table I

Demographic, lung function and morning plasma cortisol values for the 2 study groups at entry and at discharge (mean and 95 %CI).

<table>
<thead>
<tr>
<th></th>
<th>Budesonide twice-daily (n = 22)</th>
<th>Budesonide once-daily (n = 22)</th>
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<tbody>
<tr>
<td></td>
<td>entry</td>
<td>end</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>10.8 (9.5-12.1)</td>
<td>10.7 (9.6-11.8)</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>13/9</td>
<td></td>
</tr>
<tr>
<td>Mean weight (kg)</td>
<td>44.190 (37.158-51.223)</td>
<td>44.919 (37.668-52.170)</td>
</tr>
<tr>
<td>Mean height (cm)</td>
<td>141.4 (135.0-147.9)</td>
<td>142.6 (136.2-148.9)</td>
</tr>
<tr>
<td>PEFR (L/min)</td>
<td>335.5 (297.8-373.1)</td>
<td>337.6 (302.3-372.7)</td>
</tr>
<tr>
<td>VFC (% pred)</td>
<td>112.1 (106.2-118.9)</td>
<td>112.7 (106.7-118.8)</td>
</tr>
<tr>
<td>FEV1 (% pred)</td>
<td>99.9 (93.6-115.2)</td>
<td>96.2 (90.0-104.9)</td>
</tr>
<tr>
<td>FEF25-75 % (% pred)</td>
<td>97.9 (95.2-100.7)</td>
<td>97.5 (94.3-100.8)</td>
</tr>
<tr>
<td>PC20 (mg/ml)</td>
<td>1.22 (0.63-1.81)</td>
<td>1.02 (0.69-1.45)</td>
</tr>
</tbody>
</table>

![Figure 1](image1.png)  
![Figure 2](image2.png)
included 274 asthmatic children aged 6 to 17 years. It showed that budesonide turbodose (200 μg or 400 μg) once daily for 12 weeks were similarly effective to control symptoms and to improve lung function as compared to placebo. Recently, a meta-analysis on the efficacy of budesonide administered once daily compared to twice daily in patients with mild to moderate asthma found that once-daily budesonide regimen has a similar efficacy to a twice-daily regimen in doses up to 800μg per day and the authors have suggested that once-daily regimen has potential advantages in terms of patient compliance and satisfaction. In a large prospective randomized study, the long-term (up to three years) once-daily treatment with DPI budesonide (200 μg to 400 μg) decreased the risk of severe exacerbations and improves asthma control in patients with mild persistent asthma of recent onset.

Despite improved treatment protocols, asthma continues to be associated with high rates of morbidity-mortality, and poor adherence to individual treatment plans is one of the more important factors for these poor outcomes. There is an increasing consensus on the crucial role of a good adherence to asthma treatment to get the expected clinical and functional control of the disease either in the daily medical practice or in research. However, accurate assessment of medication adherence is difficult to achieve because the several factors involved (patient and parents education, family context, prescriptions, comfort, etc) and also because there is not a definitive method to measure adherence. Despite difficulties to assess adherence, an effort should be made by clinicians and researchers to objectively assess it when prescribing asthma treatment to patients. It has been shown that there is a significant discrepancy between the adherences to MDI inhaled treatment reported by mothers or children (80 %) and the calculated adherence either by canister weight (69 %) or electronic dosimeter (50 %). However, a low adherence also occurs when using inhaled steroids from a DPI with a dose monitor on the device (68 %).

It has been demonstrated that risks for poor adherence predict subsequent asthma morbidity and that most of these risks can be controlled by physicians through reducing the complexity of asthma regimens, communicating effectively with caregivers about medication use, and correcting family misconceptions about asthma medication side effects.

The effect of inhaled budesonide on lung function in asthmatic children is rather controversial and two large long term controlled studies have reported conflicting results. START using budesonide turbodose 200mcg once daily found a highly significant improvement in both prebronchodilator and postbronchodilator FEV1 % values after 1 and 3 years of the study for the treatment group as compared to placebo. However, in the CAMP study continuous daily treatment with budesonide turbodose 200mcg twice a day showed no significant effect on lung function, as measured by the FEV1 after bronchodilator use, as compared with placebo.

In the present study none of the employed modalities of inhaled budesonide had effect on changing lung function and that could be in part explained by the short term study observational time (3 months) and also because in both groups lung function was over 85 % predicted at the time they were randomized. In this regard there is some controversial information. Some authors have found significant improvement of lung function and symptoms in 3 months with DPI budesonide once daily as compared to placebo. Others using same delivery system and doses for long term have not found significant changes in lung function in asthmatic children. A similar long-term study reported that a highly significant improvement in both prebronchodilator and postbronchodilator FEV1 % values was observed after 1 and 3 years of the study for budesonide DPI treatment group compared with placebo.

In the daily practice is common to observe that many of the children with mild/moderate stable asthma have normal lung function and few symptoms, even when they could have BHR and eventually airway inflammation. It has been found that most asymptomatic asthmatics continue to exhibit BHR and signs of airway inflammation and the outcome of childhood asthma and BHR would be associated with the degree of airway inflammation and the duration of medication use.
tion of childhood asthma. A meta-analysis assessing the dose of inhaled corticosteroid and the minimum duration of treatment required to obtain a significant improvement in BHR found that high doses of inhaled corticosteroids (mean dose 1,000 μg, range 400–2,000 μg daily) decreased BHR within 2–8 weeks in patients with corticosteroid-naive asthma but remained unclear whether lower doses of inhaled corticosteroids can achieve the same results.

It is well known that every asthmatic patient should receive his/her own treatment modality designed to control the symptoms, to improve pulmonary function and decrease bronchial hyperresponsiveness and the use of rescue medication to a minimum. Thus, an important issue to consider for asthma treatment is that the dose of inhaled steroids needed to improve symptoms, improve peak flows, reduce beta-2 use, improve FEV1, improve BHR, and prevent severe exacerbations is likely to be different. It has been demonstrated that even when low and high dose of inhaled steroids had similar effects on pulmonary function and decrease bronchial hyperreactivity and the use of rescue medication to a minimum. Thus, an important issue to consider for asthma treatment is that the dose of inhaled steroids needed to improve symptoms, improve peak flows, reduce beta-2 use, improve FEV1, improve BHR, and prevent severe exacerbations is likely to be different.

It has been demonstrated that even when low and high dose of inhaled steroids had similar effects on symptoms and peak flows, the higher dose was markedly more effective at reducing severe exacerbations. This has been demonstrated that even when low and high dose of inhaled steroids had similar effects on symptoms and peak flows, the higher dose was markedly more effective at reducing severe exacerbations. Thus, the dose employed in this study (800 μg per day) was well in the range of those reported to be effective to control symptoms and improve BHR and it was safe and well tolerated in both groups.

The satisfactory clinical effect on asthma symptoms with once daily administration of budesonide through MDI plus spacer, as found in this study, may represent an advantage in terms of treatment compliance for asthmatic children, cost-effective alternative and to facilitate the long term treatment with inhaled corticosteroids in younger children who are unable to inhale medications from DPI.

Conclusion, in this study, once daily administration of budesonide by MDI plus spacer was better in controlling symptoms and improving BHR than fractioning the dose to 400 μg twice daily. The higher adherence to treatment of patients from once-daily inhaled budesonide could have accounted for the observed differences.

REFERENCES
