

REGULAR ARTICLE

Preschool children with high adherence to inhaled corticosteroids for asthma do not show behavioural problems

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ABSTRACT

Aim: To assess prevalence of behavioural problems in preschool children with asthma with electronically verified exposure to inhaled corticosteroids (ICS).

Methods: Cross-sectional study of 81 children 2–5 years of age using daily ICS for persistent asthma. During 3 months' follow-up, adherence to ICS treatment was recorded by an electronic logging device (Smart inhaler[®]). Parents completed the Child Behavior Checklist 1.5–5 years (CBCL 1.5–5) to assess behavioural problems; results were compared to a published reference group of healthy children.

Results: The median (interquartile range) adherence to ICS was 92 (78–97) %. There was no difference in total CBCL score between children with asthma on ICS (mean, [SD] 32.10 [1.99]) and the reference group (33.30 [1.87], 95% CI for difference –6.62 to 4.22). Children with asthma were more likely to have somatic complaints (95% CI for difference 0.64 to 1.96) and less likely to have anxious/depressive symptoms (95% CI for difference –1.57 to –0.25) than the reference group. CBCL scores were not significantly related to the electronically measured adherence rates.

Conclusions: Maintenance treatment with ICS, taken daily as prescribed, is not associated with an increased risk of behavioural problems in preschool children.

INTRODUCTION

Although inhaled corticosteroids (ICS) are effective in reducing asthma symptoms in preschool children (1), many parents are reluctant to provide daily maintenance medication to their child (2,3). Parental concerns about potential side effects of ICS are an important reason for such non-adherence (4). Although behavioural problems are frequently reported by parents as a potential side effect of ICS therapy (5), very few studies have examined the relationship between ICS use and behavioural problems in young children. In a general population sample, behavioural problems preceded the development of wheeze in toddlers (6). In a case control study of teenagers, anxiety and depression were more common in asthmatics than in controls (7). In two case-control studies of school-aged children, there was no significant association between ICS use and behavioural abnormalities (8,9). In none of these studies, however, was adherence to ICS taken into account, so the dose of ICS that these children were exposed to was unknown.

The aim of this study was to assess the prevalence of behavioural problems in preschool children with asthma, whose exposure to ICS was known by electronic recording of adherence. We hypothesized that the prevalence of behavioural problems in preschool children with well-

controlled asthma whilst using ICS with high adherence would be comparable to that of healthy control children.

METHODS

Setting

The data presented here were collected as part of an ongoing project on determinants of long-term adherence in 2- to 12-year-old children with asthma. In our clinic, we treat children with troublesome asthma, referred by general

Key notes

- Parents are frequently concerned about behavioural side effects of inhaled corticosteroids (ICS), particularly in young children.
- This cross-sectional study of 81 2- to 5-year-old asthmatic children with high adherence to ICS found no increased risk of behavioural problems compared to a healthy reference group.
- We hypothesize that this finding is explained by good asthma control ensured by self-management education and close follow-up.

practitioners, according to GINA guidelines (10), with special emphasis on a strong partnership with patients and parents. Patients are being followed up frequently by a paediatric asthma specialist and a paediatric asthma nurse (11), with repeated tailored education, along with an open discussion of parents' perspectives on asthma and its treatment (2). Correct inhalation technique is trained and checked extensively, and the importance of daily adherence to ICS treatment is discussed at every visit, ensuring concordance on treatment and its goals between patients/parents and the medical team (11).

Patients

Between September 2008 and June 2010, all children between 2 and 5 years of age with chronic persistent asthma, who had been treated with ICS and had been attending our hospital for regular follow-up for at least 3 months, were eligible for inclusion in the study. Exclusion criteria were limited knowledge of Dutch language and serious comorbidity. No sample size calculation was performed because we were unable to find reliable data on the prevalence of behavioural problems in preschool children with asthma.

Adherence measurements

Adherence to ICS (by metered dose inhaler/spacer combination) was monitored electronically for 3 months by a Smartinhaler® (Nexus Ltd, Auckland, New Zealand), a validated device recording date and time for each actuation of the metered dose inhaler (12). Parents were aware that adherence to ICS maintenance treatment was being monitored. Dose and dosing frequency remained unchanged during the study.

Data

Clinical and demographic information was collected by standardized questionnaire and from the medical chart (details published elsewhere) (13). At inclusion into the study, the parent accompanying the child to the clinic completed the Child Behavior Checklist 1.5–5 years (CBCL 1.5–5). The CBCL is a standardized validated questionnaire to assess emotional and behavioural problems of preschool children by parent or caregiver ratings (14). The 100 questions of the CBCL are grouped into three domains comprising a total of eight different problem axes: internalizing problems (comprising the axes emotionally reactive, anxious/depressed, somatic complaints and withdrawn), externalizing problems (attention problems and aggressive behaviour) and total problems (all eight axes, including the stand-alone axis of sleep problems).

Parents rated CBCL items as: 0 (not true); 1 (somewhat or sometimes true); and 2 (very true or often true) based on the preceding 2 months. These numbers were totalled for every axis, and mean total scores and their standard deviations were computed for all axes.

Data analysis

Adherence was calculated as the number of inhaled doses as registered by the Smartinhaler®, expressed as a

percentage of the total number of doses prescribed. For a once-daily dosing regimen, any recorded use of maintenance medication on a single day was considered a correct dose; for a twice daily regimen, each dose had to be given within an interval of 6 h of the prescribed dosing time (8 AM and 5 PM). The distribution of adherence was censored at 100% of prescribed dose.

Raw CBCL scores were computed according to the developers' instructions in the manual for the preschool forms, and compared to those of a published North American reference group of healthy children (14), similar to previous studies using this instrument (15,16), by using independent student *t*-tests with Bonferroni correction for multiple comparisons. Correlations between CBCL scores and adherence rates were assessed using Pearson's correlations coefficients.

Additional analyses of the relationship between CBCL and adherence were performed after adherence was dichotomized as $\leq 80\%$ (poor adherence) or $>80\%$ (good adherence) (17).

Multiple logistic regression analysis was performed to examine the relationship between behavioural problems and ICS adherence, adjusting for gender, socio-economic status, parental smoking, atopy and family history of asthma.

Ethical considerations

This study was approved by the hospital ethics review board; all parents provided written informed consent.

RESULTS

Between September 2008 and June 2010, 112 patients, 2–5 years of age with persistent asthma currently treated with ICS, were eligible for inclusion. Five patients were ineligible because of exclusion criteria and 17 parents declined participation, almost always because of lack of time. Of the 90 patients entering the study, 9 were lost to follow up, and 81 (90%) completed the study (Fig. 1). Characteristics of these 81 patients are presented in Table 1. Overall, patients were well controlled when entering the study (details published previously) (18).

All patients used fluticasone propionate (daily dose 125 to 500 μg) as maintenance treatment for their asthma, 6 of whom were on fluticasone-salmeterol combination therapy. The median (interquartile range; full range) 3 months adherence was 92% (78 to 97%; 41% to 100%); 60 children (74%) received more than 80% of prescribed dosages, and 46 (57%) more than 90% of prescribed dosages.

In Table 2, CBCL scores of the patients with asthma in our study are compared to those of a healthy reference group (14). There were no significant differences in CBCL scores between the groups in the three domains (internalizing problems, externalizing problems and total problems).

Children with asthma had higher scores on the axis somatic complaints ($p = 0.001$) but lower scores on anxious/depressive symptoms ($p = 0.008$) than children in the reference group (Table 2).

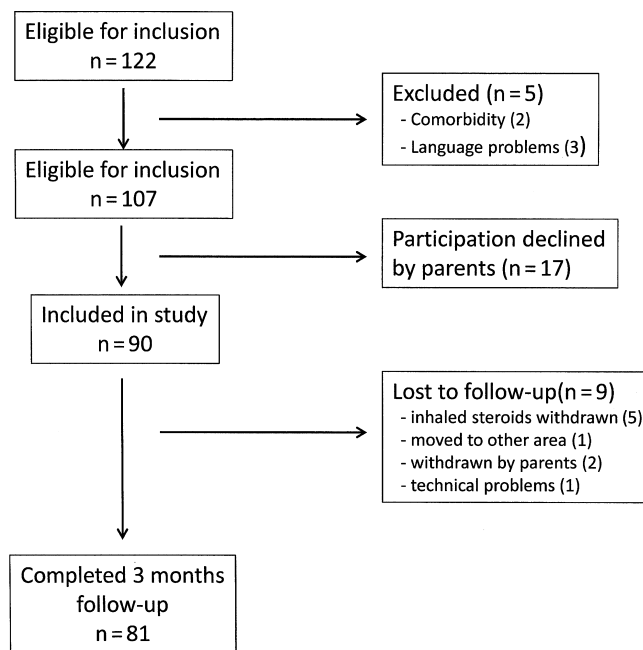


Figure 1 Patient disposition.

Table 1 Patient characteristics (n = 81)

Age in years; median (range)	4.0 (2.3–5.9)
Male gender; number (%)	48 (59%)
Family history of asthma; number (%)	33 (41%)
Parental smoking; number (%)	27 (33%)
Sensitized to aeroallergen; number (%)	34 (42%)
SES parents low; number (%)	13 (15.7%)
Middle	49 (60.4%)
High	19 (23.9%)
Emergency room visit or hospitalized in past 12 months:	
Never	55 (67.9%)
Once	19 (23.5%)
More than once	7 (8.6%)
Adherence to inhaled corticosteroids*	
Median (IQR)	92% (78–97%)

SES, socio-economic status; low SES: completion of only primary or prevocational education; middle SES: completion of secondary or vocational education; high SES: completed higher or university education.

*adherence expressed as the number of inhaled doses registered by the electronic Smartinhaler® device, expressed as a percentage of the total number of doses prescribed, censored at 100%.

Table 2 Child Behaviour Check List scores in preschool children with asthma compared to a healthy reference group (14)

Problem axis	Asthma group (n = 81)*	Reference group (n = 131)*	95% CI of difference	p**
Emotionally reactive	2.60 (0.27)	2.40 (0.22)	-0.48 to 0.88	0.56
Anxious/depressive	1.99 (0.24)	2.90 (0.23)	-1.57 to 0.25	<0.01
Somatic complaints	3.10 (0.29)	1.80 (0.19)	0.64 to 1.96	<0.01
Withdrawn	1.23 (0.14)	1.50 (0.17)	-0.72 to 0.18	0.23
Sleep problems	2.44 (0.29)	2.80 (0.24)	-1.10 to 0.38	0.34
Attention problems	2.49 (0.22)	2.50 (0.19)	-0.58 to 0.56	0.97
Aggressive behaviour	9.00 (0.69)	10.40 (0.64)	-3.26 to 0.46	0.14
Internalizing problems	8.93 (0.68)	8.60 (0.62)	-1.49 to 2.15	0.74
Externalizing problems	11.49 (0.84)	12.90 (0.77)	-3.66 to 0.84	0.22
Total score	32.10 (1.99)	33.30 (1.87)	-6.62 to 4.22	0.66

*Data given as mean (SEM); higher scores indicate more behavioural problems.

**Student's t-test.

Correlations between adherence to ICS and CBCL scores on the seven axes, the two domains and the total score were weak (ranging from -0.09 to 0.0) and nonsignificant (all p-values > 0.40). Similarly, there were no significant differences in CBCL scores between children with good adherence (>80% of prescribed doses) and poor adherence (≤80%) (all p-values > 0.3).

In multiple logistic regression analyses, CBCL scores (axis, domain, and total scores) were not significantly associated with ICS adherence (dichotomized as good or poor

adherence), adjusted for gender, socio-economic status, parental smoking, atopy and family history of asthma (all p-values > 0.26).

DISCUSSION

This study shows that preschool children with persistent but well-controlled asthma, using daily ICS therapy as confirmed by electronically measured adherence, have a comparable risk of behavioural problems as a healthy reference group without asthma. This finding suggests that asthma treatment with ICS does not have a deleterious effect on preschool children's behaviour.

Adherence to prescribed daily maintenance treatment with ICS was remarkably high, with a median of more than 90% of prescribed dosages actually taken. This is in contrast with previous studies in school-aged children and adolescents with asthma, where median adherence ranges from 40 to 70% (18,19). Because the children in this study were consecutive patients with a scheduled follow-up appointment at our clinic, it is unlikely that our study population was a selective sample of highly adherent parents.

The increased risk of somatic complaints (which include dizziness, tiredness, headaches and stomach aches) in the asthma group was not unexpected. These can be a result of asthma itself or its comorbidity (20). Because our study was performed in a hospital-based setting, the risk of more severe asthma and comorbidity is likely to be higher than in a general-population-based sample of asthmatic children. Similar results were found in a population of school-aged children and adolescents with difficult to treat asthma (21).

In contrast to previous studies, however, the rate of behavioural problems in our sample of preschool children with persistent asthma using daily ICS medication was comparable to that of a healthy reference group, and the risk of anxious and depressive symptoms was even lower than that of control children (Table 2). Previous studies showed more anxious/depressive symptoms, and more internalizing problems, in children with asthma compared to healthy controls (22–24). Selective recruitment of healthy children without behavioural problems is unlikely to be responsible for this finding, because our study population was a representative sample of preschool children with persistent asthma using ICS followed up at a hospital-based paediatric asthma clinic (13). These children were not newly referred, but had all been on ICS maintenance therapy, and under our comprehensive asthma care, for at least 3 months. We hypothesize, therefore, that the good asthma control associated with high adherence to ICS medication in our study population reduced the deleterious effects of asthma on behaviour observed in previous studies where asthma was less well controlled (22–24).

After an initial case report published more than 20 years ago (25), the perception that ICS can have adverse effects on children's behaviour has gained widespread support among parents. This is illustrated by the recent finding that more than 20% of reported side effects of ICS in a national Dutch pharmacovigilance database concerned behavioural problems (5). Our study, together with two recently published case-control studies (8,9), however, did not find any association between ICS use and behavioural problems in children. Although this does not exclude behavioural side effect in isolated cases, these findings argue against behavioural problems as a relevant and common side effect of ICS therapy in young children.

The main strength of our study is that we have measured therapy adherence electronically with a validated logger device (12). With the very high adherence measured, this ensures that the patients in our study were actually exposed to daily ICS. The absence of behavioural side effects in this

study, therefore, strongly supports the safety of ICS in this regard.

We acknowledge the following limitations of our study. First, we used the CBCL, a parent-completed questionnaire, instead of a formal psychological evaluation of the children themselves. However, the CBCL is generally agreed to be a useful screening instrument for behavioural problems in children and has been used as such extensively in previous research, including neonatal intensive care graduates, post-term births, and as a screening tool in general population studies (26–28). Second, we used data from a previously published healthy reference group instead of a purposefully selected group of matched controls. Although this approach weakens the generalizability of our findings, it is more feasible and has been used in earlier studies. Thirdly, this was a cross-sectional study; more detailed information on the relationship between ICS use and behavioural problems should be obtained from prospective cohort studies. Finally, this analysis was performed in an ongoing study not specifically designed for the purpose of examining the relationship between ICS use and children's behaviour. Our results, therefore, should be interpreted with some caution.

In conclusion, our study shows that maintenance treatment with ICS with high adherence is not associated with an increased risk of behavioural problems in preschool children with well-controlled asthma. This suggests that behavioural problems observed in earlier studies of children with asthma may be due to uncontrolled disease. Further studies are needed to test this hypothesis.

CONFLICT OF INTERESTS

The authors declare no competing interests.

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