

Original article

Local side-effects of inhaled corticosteroids in asthmatic children: influence of drug, dose, age, and device

Background: The objective was to investigate the local side-effects of inhaled corticosteroids (ICS) in daily life in asthmatic children, particularly the younger ones, by an observational prospective cross-sectional cohort study.

Methods: Asthmatic children ($n=639$, 75.9 ± 48.9 months, 61.3% boys), treated with beclomethasone dipropionate (BDP) (721.0 ± 287.3 μg per day) or budesonide (BUD) (835.5 ± 684.9 μg per day) for at least 1 month, were recruited at the time of a scheduled visit. Local side-effects were researched by questionnaire (cough during inhalation, hoarseness, dysphonia, and thirsty feeling) and clinical examination (perioral dermatitis, oral candidiasis, and tongue hypertrophy).

Results: Exactly 63.3% of the children aged under 6 years and 59.5% of the older ones reported one local side-effect. Cough (39.7%) was dependent on young age, use of BDP, and mainly use of spacer device, with an OR of 4.7 (95% CI: 2.7–8.2). Thirsty feeling (21.9%) and hoarseness (14.1%) occurred in children using ICS and long-acting β_2 -agonists. Dysphonia (11.1%) was favored by high doses of BDP and BUD, and by inhalation from spacer devices or nebulizers. No factor favored oral candidiasis (10.7%). Perioral dermatitis (2.9%) and tongue hypertrophy (0.1%) were associated with nebulization.

Conclusions: Local side-effects of ICS are common in asthmatic children of all ages, and the device used constitutes the most influential factor.

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Widely recommended for controlling airway inflammation in adult or pediatric asthma (1, 2), inhaled corticosteroids (ICS) can induce lateral effects, particularly systemic side-effects (3–6), that the practitioner has to limit by determining the lowest dose of ICS compatible with good disease control and, if possible, by prescribing doses of ICS which do not have significant systemic effect, i.e., doses of less than 400 μg a day (7, 8). Compared with the systemic side-effects, local side-effects of ICS are usually considered to constitute infrequent and minor problems. These adverse effects (hoarseness, dysphonia, oral candidiasis, cough, etc.) have been very well documented in adults, and it has been shown that they cause immediate clinical discomfort for patients and potentially alter compliance to treatment (10–24). Publications on the local side-effects of ICS in children are rare (25–28), and, to our knowledge, whereas ICS are increasingly prescribed for young children, there are no published data concerning their local effects in this age bracket.

Abbreviations. BDP: beclomethasone dipropionate; BUD: budesonide; ICS: inhaled corticosteroids; pMDI: pressurized metered-dose inhaler.

The aim of this observational prospective cross-sectional multicenter survey was to compare in an unselected group of asthmatic children from infancy to childhood and treated with ICS the influence of the drug, the dose, the age, and the device in daily life with respect to ICS-induced local side-effects.

Material and methods

Study design

Patients were prospectively recruited between April 1998 and April 1999 from eight pediatric pulmonary clinics located throughout France and all attached to university hospitals. They were consecutively enrolled at the time of a scheduled visit, the families having no prior warning of the study. Inclusion criteria were as follows: to have asthma as defined by the International Consensus (2), to be regularly and correctly treated with inhaled beclomethasone dipropionate (BDP) or budesonide (BUD) for at least 1 month, and not to have been treated with oral steroids or antibiotics for 1 month before the study.

Data concerning the patient (age and sex), characteristics of ICS therapy (drug, daily dose, number of daily administrations, means of delivery, use of a face mask for spacer device or nebulization, duration of treatment, and practice of mouth rinsing), and local side-effects observed in the previous month were collected both by questionnaire and clinical examination. Classical side-effects, such as

dysphonia, hoarseness, and cough during inhalation were sought for. The frequency of these side-effects (never, occasionally, or daily, at each inhalation) was specified. As some investigators had noted in their clinical practice that children needed to drink after inhaling their treatment, we also looked for thirsty feeling after ICS delivery. Mouth rinsing was considered to be appropriate when performed after each ICS inhalation. Oral candidiasis has been considered when thrush was clinically observed. Perioral dermatitis was defined by dryness of the skin around the mouth. The inhaled doses of ICS were also considered, low doses being defined as less than or equal to 500 µg/day BDP or 400 µg/day BUD. The population was divided into two groups: the young children aged less than 6 years and the others. Oral informed consent was obtained from all children and parents, as recommended by the ethics committee. No child or family refused to participate in the study.

Statistical analysis

The SPSS, Version 8.01, was used for the analysis. The usual statistical tests were performed for univariate analysis. Qualitative variables were compared between groups by the chi-square test, and quantitative variables were compared by analysis of variance or *t*-test. A forward logistic regression (Wald test) was performed to adjust the determinants of the data for any confounding factors. We included in the multivariate analysis variables with a *P* value of <0.25 in the univariate analysis and clinically relevant variables. A *P* value lower than 0.05 was considered statistically significant.

Results

Patients and treatments

The study concerned 639 asthmatic children (61.3% boys), aged 75.9 ± 48.9 months (range: 3 months to 16 years; 51.6% of the children were aged less than 6 years). A long-acting β_2 -agonist was associated in 142 patients, 78.1% of them being older than 6 years. Characteristics of the ICS treatments are described in Table 1. The mean duration of the ICS treatment was 15.1 ± 14.0 months. ICS were mainly delivered once (16.1% of cases) or twice a day (81.4% of cases), without difference between the drugs (*P*=0.89). BDP or BUD was administered to 82% of the young children from pMDIs actuated through small-volume spacer devices (Babyhaler® [*n*=209], Aerochamber® [*n*=2], or metallic NES-Spacer® [*n*=36]), and 14% were treated with nebulized BUD. The devices used by older children were Turbuhaler® (47.6%), pMDIs delivered from a spacer device (34.3%; Babyhaler [*n*=47], Volumatic® [*n*=46], Nebuhaler® [*n*=3], and Aerochamber [*n*=4]), and pMDIs alone or Autohaler® (16%). Compared to BUD, BDP was used significantly more in young children. These results are probably due to the choice of the device according to the age of the children and the ability of the device chosen to deliver BDP or BUD. As the NES-Spacer®, a spacer device to use with BUD, has been recently available in France, BDP was recommended with Babyhaler in 62.9% of the young children. Conversely, BUD was administered in 64.9% of the older children, as Turbuhaler was the only ICS dry-powder inhaler available during the study period.

The daily delivered dose was dependent on the drug (Table 1) and on the age (daily dose of 843.6 ± 587.9 µg/day in children <6 years vs 686.1 ± 344.8 µg/day in children >6 years; *P*=0.0001). This unexpected result was explained by the high nebulized dose of BUD used in young children (50/52 children with doses higher than 1000 µg/day). Low doses of ICS were prescribed for 311 children (49.8%).

The face mask was used for 91.4% of the patients treated with Babyhaler (*n*=256) or NES-Spacer (*n*=40), and for 55.9% of those with nebulized BUD. Finally, children and parents stated that the mouth was rinsed after each ICS delivery in 46.7% of cases.

Local side-effects of ICS

At least one local side-effect was reported in 61.5% of the children (*n*=393). Altogether, side-effects were as follows: cough during inhalation (*n*=254, 39.7%), thirsty feeling (*n*=140, 21.9%), hoarseness (*n*=90, 14.1%), dysphonia (*n*=71, 11.1%), clinical oral candidiasis (*n*=69, 10.7%), perioral dermatitis (*n*=19, 2.9%), and tongue hypertrophy (*n*=1, 0.1%). Cough was observed daily or at each inhalation in 93% of cases. Conversely, hoarseness and dysphonia were reported occasionally.

Factors influencing the occurrence of local side-effects

Influence of drug and dose. BDP (Table 2) induced more side-effects than BUD at either low or high doses (*P*=0.0001). Only dysphonia tended to be related to the ICS dose and occurred less frequently with low than high doses of BUD (*P*=0.05).

Influence of age. Children aged under 6 years had as many side-effects as children aged more than 6 years (63.3% vs 59.5%; *P*=0.32). This result was unchanged when thirsty feeling, difficult to estimate in young patients, was excluded (54.9% vs 45.1%; *P*=0.07). Cough and perioral dermatitis were more often reported in the young than in the older children (respectively, 47.3% vs 31.7%, *P*=0.0001 and 4.6% vs 1.3%, *P*=0.01). Conversely, hoarseness was less frequent in the young than in the older patients (10.3% vs 18.1%; *P*=0.005).

Influence of device. The influence of device on local side-effects is displayed in Table 3. To obtain a sufficient number of children per group for statistical analysis, the pMDIs and Autohaler groups were pooled. The incidence of cough during inhalation was doubled when a spacer device rather than another device was used: 53.8% vs 26.5% in the BDP group (*P*=0.0001), and 53.2% vs 17.9% in the BUD group (*P*=0.0001). Occurrence of this side-effect was not linked to the drug used. Children coughing during

Table 1. Characteristics of inhaled corticosteroid therapy in 639 children with asthma (results are compared by *t*-test for age, daily dose, and duration of treatment, and by chi-square test for other data)

	Beclomethasone dipropionate (<i>n</i> =380)	Budesonide (<i>n</i> =259)	<i>P</i> value
Age (months)	64.6 ± 41.7	92.6 ± 53.8	0.0001
Proportion of boys	<i>n</i> =243 (64.8%)	<i>n</i> =143 (56.1%)	0.02
Daily dose (µg/day)	721.0 ± 287.3	835.5 ± 684.9	0.0001
Duration of treatment (months)	15.2 ± 13.9	15.0 ± 14.1	0.68
Delivery b.i.d.	<i>n</i> =307 (81.6%)	<i>n</i> =209 (81.0%)	0.89
Type of device			
pMDI* plus spacer device	<i>n</i> =331 (87.1%)	<i>n</i> =47 (18.1%)	0.0001
pMDI*	<i>n</i> =24 (6.3%)	<i>n</i> =6 (2.3%)	
Autohaler	<i>n</i> =25 (6.6%)	—	
Dry-powder inhaler	—	<i>n</i> =154 (59.5%)	
Nebulizer	—	<i>n</i> =52 (20.1%)	

* pMDI: pressurized metered-dose inhaler.

inhalation had significantly less hoarseness and dysphonia than children who did not cough ($P=0.009$ and $P=0.0001$, respectively). Dysphonia was more frequent with a pMDI with a spacer device or a nebulizer than with a Turbuhaler®, a pMDI alone, or an Autohaler ($P=0.02$). Perioral dermatitis occurred only in children using a spacer device with face mask ($n=14/268$, 5.2%) or a nebulizer with face mask or without face mask or mouthpiece ($n=5/35$, 14.3%). Tongue hypertrophy was observed in one 4-month-old child treated with nebulized BUD (1500 µg/day for 6 months).

Influence of other factors. Some local side-effects were significantly associated with risk factors other than age, drug, dose, and device: thirsty feeling was linked with use of long-acting β_2 -agonists, and hoarseness was associated with duration of treatment, multiple daily inhalations of ICS, and use of long-acting β_2 -agonists. We were unable to demonstrate a protective effect of mouth rinsing on the occurrence of oral candidiasis.

Multivariate analysis. Adjusted to sex, age, drug, dose, and device, cough during inhalation depended on the use of a spacer device with an odds ratio of 4.7 (95% CI: 2.7–8.2).

Table 2. Main local side-effects of inhaled corticosteroid therapy in 639 asthmatic children treated with beclomethasone dipropionate or budesonide for at least 1 month (results are compared by chi-square test)

	Beclomethasone dipropionate (<i>n</i> =380)	Budesonide (<i>n</i> =259)	<i>P</i> value
Cough during inhalation	<i>n</i> =191 (50.3%)	<i>n</i> =63 (24.3%)	0.0001
Thirsty feeling	<i>n</i> =90 (23.7%)	<i>n</i> =50 (19.3%)	0.18
Hoarseness	<i>n</i> =60 (15.8%)	<i>n</i> =30 (11.6%)	0.13
Oral candidiasis	<i>n</i> =41 (10.7%)	<i>n</i> =28 (10.8%)	0.91
Dysphonia	<i>n</i> =45 (11.8%)	<i>n</i> =26 (10.0%)	0.50

Discussion

Our multicenter study showed that more than 60% of the asthmatic children and infants treated with ICS were affected by at least one local side-effect in daily life. This high incidence of ICS-induced adverse events in childhood contrasts with the results of a recent questionnaire survey which estimated that only 3% of adults and adolescents developed frequent local oropharyngeal side-effects (28). This unexpected gap between both reports might be due either to our hospital-based population of children with moderate to severe asthma requiring relatively high doses of ICS or to the high incidence of cough in the youngest children.

Observed in more than a third of the children, the occurrence of cough during inhalation of ICS clearly raises questions about the lung deposition of the drug and the efficacy of the treatment. In adults, cough has been correlated with worse control of asthma (12). The causes proposed to explain this side-effect were as follows: clinical manifestation of asthma, toxic role of the inhaled excipients (oleic acid) from pMDIs, and nonspecific irritant effects of ICS (9, 13, 15, 29). By contrast with previous adult studies (12, 21), our report demonstrated that cough was only a spacer device-dependent side-effect. This finding is of clinical relevance, as the occurrence of cough in children suggests that one should change the device used to deliver ICS rather than the ICS itself.

Hoarseness was rarely described in childhood asthma (27). Conversely, in adults, a dose-dependent hoarseness has been reported in 34% of patients treated with BDP or BUD (21). Other studies, also in adults, have reported an increased risk of hoarseness with fluticasone propionate compared to BDP, and with pMDIs compared to dry-powder inhalers (17–19, 22). In our study, hoarseness was less common than in adults and occurred in older children treated for a long time and using long-acting β_2 -agonists. The exact mechanism of hoarseness is unknown. Oropharyngeal deposition may play a role, as supported by the decreased incidence of

Table 3. Effect of device on occurrence of inhaled corticosteroid-induced local side-effects in 639 children with asthma (results were compared by ANOVA for age, daily dose, and duration of treatment, and by chi-square test for other data)

	pMDI* or Autohaler (n=55)	pMDI* plus spacer device (n=378)	Dry-powder inhaler (n=154)	Nebulizer (n=52)	P value
Age (months)	125.9 ± 37.6	54.3 ± 33.7	126.2 ± 34.4	31.6 ± 25.7	0.0001
Daily dose (µg/day)	590.0 ± 273.2	718.9 ± 283.7	590.9 ± 312.9	1830.7 ± 871.7	0.0001
Duration of treatment (months)	19.7 ± 16.1	14.0 ± 13.1	18.6 ± 15.9	8.9 ± 6.9	0.0001
Cough during inhalation	n=14 (25.5%)	n=203 (53.7%)	n=27 (17.5%)	n=10 (19.2%)	0.0001
Thirsty feeling	n=18 (32.7%)	n=80 (21.2%)	n=29 (18.8%)	n=13 (25.0%)	0.17
Hoarseness	n=10 (18.2%)	n=57 (15.1%)	n=19 (12.3%)	n=4 (7.7%)	0.36
Oral candidiasis	n=7 (13.2%)	n=38 (10.6%)	n=17 (11.7%)	n=7 (15.6%)	0.76
Dysphonia	n=2 (3.6%)	n=47 (12.5%)	n=12 (7.8%)	n=10 (19.6%)	0.02

* pMDI: pressurized metered-dose inhaler.

hoarseness when children coughed during inhalation. However, the relationship of this symptom with ICS inhalation is unclear, as Agertoft et al. (27) showed a comparable incidence of hoarseness in healthy controls and long-term BUD Turbuhaler-treated children.

Oral candidiasis has been widely studied in ICS therapy and has an incidence of 0–77% due to differences in diagnostic criteria (10, 14, 16, 21, 24). This side-effect may be due to a decreased local immunity or to an increase in salivary glucose, which stimulates *Candida albicans* growth (16, 30). In our study, where clinical criteria were used, oral candidiasis was observed in 10% of the patients. However, the frequency of candidiasis may be underestimated, as Shaw & Edmunds (24) isolated *C. albicans* in 29% of healthy children and 45% of children treated with BDP, whereas only one case of thrush was reported in the treated group. Moreover, we were unable to confirm the well-known risk factors (high doses of ICS or multiple daily administrations) or protective factors (use of a spacer device with ICS or mouth rinsing after drug delivery) of oral candidiasis (10, 14, 16).

Dysphonia is probably caused by cortisone myopathy, and not by laryngeal candidiasis (11, 16). Indeed, Toogood et al. (10) showed that BDP, but not chlorofluorocarbon or excipients, could induce dysphonia. In a similar manner, dysphonia was reported with the BUD Turbuhaler, which contains no excipients or propellant (15, 18, 22, 23). Lastly, dysphonia ceased when ICS was stopped (11, 18). As in adults (15, 18, 22, 23), dysphonia was more frequently observed in children using a spacer device or a nebulizer. The possible protective effect of dry-powder inhalers, pMDIs, and Autohaler, in comparison with spacer devices, might be related to the position of the vocal cords, which are open during inhalation against resistance (20). ICS have been shown to induce a dose-dependent dysphonia in asthmatic adults (3, 10, 17, 19, 21). In our study, only a trend between low- and high-dose groups of BUD was observed.

Perioral dermatitis was infrequent in children and depended on whether they used a device equipped

with face mask or a nebulizer without face mask or mouthpiece. These results are in accordance with those previously reported by Held et al. (26) and support the hypothesis of a direct local effect of ICS on the facial skin. In severe cases of perioral dermatitis, the use of topical erythromycin or metronidazole can be recommended (26).

One case of reversible tongue hypertrophy was described in a young patient treated with nebulized BUD. Case reports were previously described in young children treated with nebulized BDP for bronchopulmonary dysplasia (25). Tongue hypertrophy was related to a direct effect of ICS, inducing either tongue muscle hypertrophy or local fat accumulation, rather than hypothyroidism or local infection.

Thirsty feeling after ICS delivery was found in more than one child in five in our study. The only risk factor for thirsty feeling was a combined treatment with ICS and long-acting β_2 -agonists. This feeling may correspond to one of the first symptoms of oral candidiasis or may be caused by throat irritation.

In conclusion, if the instruction of the parents and the children is an essential part of treatment of asthmatic children with ICS, the detection of local side-effects is also important because the local side-effects of ICS are common in patients of all ages. These adverse events are not drug-dependent, but cough, dysphonia, perioral dermatitis, and tongue hypertrophy are device-dependent, with important therapeutic implications for the practitioner. Thirsty feeling, hoarseness, and oral candidiasis are less treatable through modifications of ICS therapy.

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