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Minor acute effect of an inhaled corticosteroid (budesonide) on bronchial hyperresponsiveness to methacholine in children with asthma

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ABSTRACT: Several studies have shown that long-term administration of inhaled corticosteroid reduces airway hyperresponsiveness. This study was performed in order to exclude an acute effect of inhaled corticosteroid.

In a double-blind, randomized, cross-over study, children with asthma, who had never used inhaled or oral corticosteroid, received a single dose of 0.8 mg budesonide or placebo on two separate days, with an interval of at least 48 h. On each test day, baseline forced expiratory volume in one second (FEV_1) and methacholine responsiveness (expressed as provocative dose producing a 20% fall in FEV_1 (PD_{20}) to methacholine, in doubling dose) were measured. Both measurements were repeated 2 and 5 h after administration of the drug.

Twenty children were included in the study. FEV_1 showed a mean increase of 1% at 5 h on the budesonide day, and a decrease of 2% on the placebo day (p=0.01). PD_{20} increased by 0.1 doubling dose on the budesonide day, and decreased by 0.4 doubling dose on the placebo day. These changes are within the measurement variation (p=0.06).

We conclude that a single dose of 0.8 mg budesonide has a minor effect on methacholine responsiveness 5 h after administration in children with asthma. It is unlikely that such an effect interferes with the interpretation of data collected in long-term studies.

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Asthma is characterized by airway hyperresponsiveness (AHR) to methacholine or histamine. Airway inflammation plays a central role in asthma, and is associated with AHR [1]. Several studies have shown that inhaled corticosteroid (ICS) gradually reduces AHR, after weeks or months [2], possibly by its anti-inflammatory action [3]. In these studies, it was assumed that ICS has no acute effect on AHR. However, in children, this was never investigated.

If an acute effect exists, this might hamper the interpretation of the effect of long-term drug administration on AHR. This acute effect, if any, is not likely to be pronounced, because protein synthesis, which will be activated by corticosteroid, is a slow process [4]. We investigated the acute effect of a single dose of inhaled corticosteroid on airway responsiveness, in order to test this assumption.

Patients

Twenty children with a history of asthma were selected from the out-patient clinic of the subdivision of Paediatric Respiratory Medicine of the Sophia Children's Hospital. They were atopic for one or more allergens and had been in a stable condition for at least 4 weeks. Their forced expiratory volume in one second (FEV_1) was >70% of predicted, and AHR expressed as the provocative dose of methacholine which caused a fall in FEV_1 of 20% (PD_{20} methacholine) was ≤150 nmol, *i.e.* more than two standard deviations below the mean value in healthy children [5]. The patients had never used inhaled corticosteroid before, and were treated with cromoglycate and/or inhaled $beta_2$-agonist. All participants and their parents gave their informed consent. The study was approved by the Medical Ethics Committee of the hospital. Patient characteristics are shown in table 1.

Methods

All medication was stopped 8 h before each test day. FEV_1 was measured using a water-sealed spirometer, according to the European Community for Coal and Steel (ECCS) recommendations [6]. The largest value resulting from 3–5 attempts was recorded. Reference values were those of ZAPLETAL *et al.* [7]. PD_{20} methacholine was measured by inhalation of methacholine in doubling doses

(DD), according to a standard protocol [8]. Methacholine solutions were stored at 4°C and nebulized at room temperature. Methacholine was nebulized with a deVilbiss 646 nebulizer, with 5 ml per vial. The nebulizer was attached to a Rosenthal-French dosimeter, driven by air at 138 kPa (20 psi). The aerosol was delivered directly to the mouth, *via* a mouth tube. The child inspired as slowly as possible from functional residual capacity to total lung capacity, and held the breath for 5–10 s before expiration. During inspiration, the dosimeter was triggered for 0.6 s. A total of 20 µl of aerosolized solution was delivered to the mouth, in four consecutive breaths. After baseline measurement of FEV_1 subjects started with saline, followed by increasing doses of methacholine from 0.25–64 nmol. FEV_1 was measured 3 min after saline and after each dose of methacholine.

Table 1. – Patient characteristics

Pt no.	Sex	Age yrs	FEV_1 % pred	Daily medication n×mg
1	M	7	90	DSCG 2×5, S 2×0.1
2	M	10	86	T 0.25 i.n.
3	M	8	111	DSCG 3×5, T 0.25 i.n.
4	M	13	74	DSCG 3×5, T 3×0.25
5	M	8	78	DSCG 2×10, S 0.1 i.n.
6	M	10	94	DSCG 3×10, T 0.25 i.n.
7	M	7	81	S 0.1 i.n.
8	F	7	107	S 0.1 i.n.
9	M	11	87	DSCG i.n.
10	M	7	96	DSCG 3×10, S 0.1 i.n.
11	F	9	84	DSCG 3×5
12	M	9	90	T 0.5 i.n.
13	M	10	106	T 0.5 i.n.
14	F	10	105	DSCG 2×5, S 0.1 i.n.
15	F	10	103	DSCG 3×20, T 0.5 i.n.
16	M	10	83	DSCG 3×5, S 0.1 i.n.
17	F	9	109	T 0.5 i.n.
18	M	11	91	T 0.5 i.n.
19	M	7	71	DSCG 3×10, S 4×0.2
20	M	8	98	DSCG 2×5, T 2×0.5

DSCG: sodium cromoglycate; S: salbutamol; T: terbutaline; i.n.: if needed.

The test was stopped when FEV_1 had fallen by 20% from the prechallenge value. PD_{20} methacholine was calculated by a computer programme, which used linear interpolation.

The study was double-blind, randomized, placebo-controlled, and cross-over. Randomization was performed by allocating each patient to the next number on a randomization list, which dictated the sequence in which drugs were delivered. Patients were tested on two different days within one week, with an interval of at least 48 h. Baseline measurements of FEV_1 and PD_{20} were performed on both days. At least 60 min after the last dose of methacholine (when FEV_1 had returned to within 10% of baseline) patients received 0.8 mg budesonide or placebo, in random order. In an earlier study, we showed that with this design the reproducibility of the test is within 1 DD [8]. Budesonide and placebo were administered using a metered dose inhaler with a spacer (Nebuhaler®). One puff of budesonide contained 0.2 mg. During a slow inspiration from functional residual capacity to total lung capacity, budesonide or placebo was inhaled immediately after actuation. Subsequently, the breath was held for about 10 s before expiration. This was repeated three times. Two and five hours after inhalation of budesonide or placebo, methacholine challenges were repeated. The complete test procedure took 7–8 h. Power calculations led to a study size of 20 patients. At alpha=0.05 (two-sided paired t-test), the power for a difference of means of 0.75 SD equals 90%.

Statistical analysis

PD_{20} measurements were evaluated after logarithmic transformation. Comparisons of baseline FEV_1 and the logarithm of PD_{20} between the two study days were made using paired t-tests. Results after treatment with budesonide and placebo were compared using t-tests, as appropriate for cross-over studies [9]. Repeated measurements analysis of variance (ANOVA) was used to evaluate changes over time. The limit of statistical significance was set at p=0.05 (two-sided).

Results

There was no statistically significant difference in baseline values of FEV_1 and PD_{20} between the two test days (table 2). The change of FEV_1 in % from baseline is reflected in figure 1, and shows a small but significant difference (p=0.01) at 5 h between the budesonide day (when a mean increase of 1% compared to baseline was seen) and the placebo day (when there was a decrease of 2%). Changes in PD_{20} from baseline expressed as DD, are shown in figure 2. After 2 h, no significant change had occurred with either treatment. Five hours after budesonide, a mean±SEM increase in PD_{20} of 0.1±0.2 DD was found, while after placebo a mean decrease of 0.4±0.2 DD occurred. Both changes were within the individual measurement variation [10]. The difference of 0.5 DD between treatments was only marginally significant (p=0.06). Neither baseline FEV_1 nor baseline PD_{20} was significantly correlated with the change in PD_{20}.

Table 2. – Baseline data

	Budesonide	Placebo
FEV_1 *l**	1.82 (0.34)	1.80 (0.33)
FEV_1 % pred*	92 (11)	92 (13)
PD_{20} nmol #	27 (5–81)	27 (8–270)

FEV_1: forced expiratory volume in one second; PD_{20}: provocative dose produced a 20% fall in FEV_1. *: mean (SD); #: geometric mean (range).

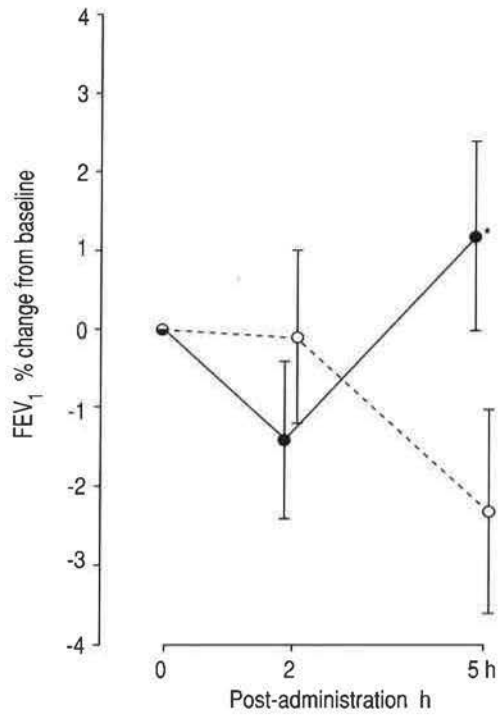

Fig. 1. – FEV_1 as % change from baseline within the same day *versus* time after drug administration. Data given are mean±SEM. FEV_1: forced expiratory volume in one second. —●—: budesonide; --○--: placebo. *: p=0.01 *vs* placebo.

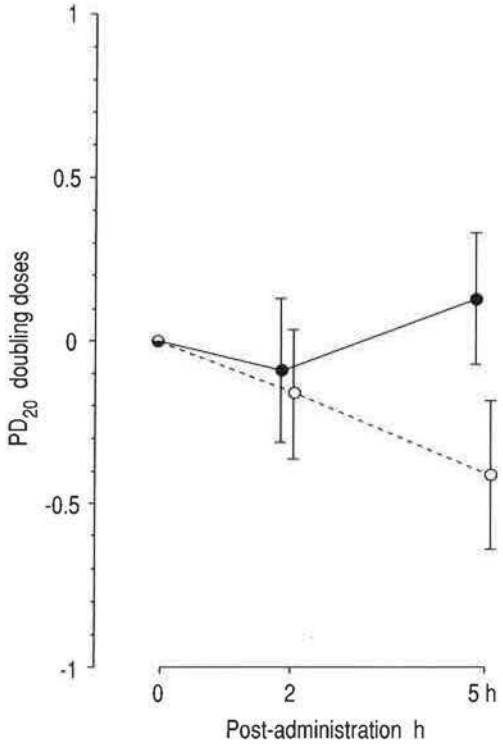

Fig. 2. – Change in PD_{20} from baseline within the same day after drug administration as doubling dose. Data given as mean±SEM. PD_{20}: provocative dose of methacholine producing a 20% fall in forced expiratory volume in one second from baseline. —●—: budesonide;--○--: placebo.

This applies to both 2 and 5 h after treatment. Individual data show an increase of PD_{20} in 10, a decrease in 4, and no change in 6 patients, after budesonide. These numbers are 3, 10 and 7, respectively, after placebo. Analysis of the data according to the sequence in which both treatments were given revealed no differences. This excludes a carry-over effect.

Discussion

This study shows a minor effect of a single dose of inhaled corticosteroid on AHR to methacholine 5 h after administration. A small increase in FEV_1 was also seen. These changes were within the individual measurement variation.

In asthma, inflammation of the airways seems to be a persistent feature, even in patients with mild symptoms [11, 12]. AHR to a number of stimuli, such as histamine and methacholine, is a characteristic of asthma, and there is an association between AHR and airway inflammation [1]. Nowadays, inhaled corticosteroids are the most effective drugs, probably due to their anti-inflammatory properties. Long-term administration of inhaled corticosteroid suppresses the inflammatory reaction [3] and causes a decrease in AHR to histamine and methacholine [2]. The effect of inhaled corticosteroid on the degree of AHR is time- and dose-related [13]. The long-term effect of inhaled corticosteroid on AHR might be misinterpreted if these drugs also had an acute effect on AHR. This has never been investigated in children with asthma.

Recently, VATHENEN *et al.* [14] studied the acute effect of a single dose of inhaled corticosteroid on AHR to histamine. In a double-blind, placebo-controlled study they compared the effect of 800 μg budesonide to placebo, in 20 adult patients with asthma. They measured PD_{20} to histamine before and 1, 6, 12 and 24 h after administration of the drug. They found a small but significant increase in median FEV_1 (+0.2 *l*, 95% confidence interval 0.05–0.40) and in median PD_{20} histamine (+1 DD, 95% confidence interval 0.2–1.6) after budesonide, which was maximal at 6 h. These differences were statistically significant at the 1% level.

We selected children with mild asthma, who had never used inhaled or oral corticosteroid. Their treatment consisted of $beta_2$-agonist on demand and/or regular cromoglycate. They were all hyperresponsive to methacholine. The interval between the two test days was at least 48 h, in order to prevent a carry-over effect of inhaled corticosteroid in the patients who received placebo on the second day. No such carry-over effect was found. The decrease in PD_{20} during the placebo day is fully attributable to the diurnal variation in airway responsiveness. VAN AALDEREN *et al.* [15] showed a spontaneous decrease in PC_{20} of 0.5 DD between 8.00 a.m. and 4.00 p.m., in two groups of children with asthma. The slight increase of PD_{20} on the budesonide day suggests that even a single dose of inhaled corticosteroid diminishes the diurnal variation in airway responsiveness. The change in PD_{20} in this study is less than that found by VATHENEN

et al. [14], who used the same dose of inhaled corticosteroid. We measured AHR 2 and 5 h after drug administration, so that the possibility remains that the maximal effect was missed because we do not have data over a longer time interval. We would have preferred to measure AHR for a longer period than 2–5 h after drug administration, or to determine AHR in the morning after drug administration the night before. This was, however, not feasible, because children of this age would not co-operate if the study took longer than 7–8 h, or if they had to come twice on two consecutive days. Indeed most children needed encouragement for the last AHR measurement on a test day.

ELLUL-MICALLEF [16] showed that a single dose of budesonide of 1.6 mg or 0.1 mg has an acute effect on peak expiratory flow rate, which is maximal after 5–8 h, and lasts about 12 h. In another study, the immediate effect of 1.6 mg budesonide on FEV_1 was maximal after 5 h, and showed a plateau until at least 9 h after administration [17]. This effect probably also disappeared after 12 h. The results of these studies indicate that the maximal effect of inhaled corticosteroid occurs within 5 h after administration. The reason that we studied the effect of 0.8 mg budesonide, which is higher than the dose usually prescribed, is that we wanted to avoid the risk of missing an acute effect due to underdosing. We conclude that it is unlikely that the results of long-term studies on the effect of inhaled corticosteroid on AHR are biased by an acute drug effect.

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