

Switching from systemic steroids to ciclesonide restores the hypothalamic pituitary-adrenal axis

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Abstract

Introduction: Treatment of difficult asthma with oral corticosteroids (OCS) may suppress the hypothalamic-pituitary-adrenal axis.

Aim: In this study we have checked if the substitution of OCS with very high doses of ciclesonide may restore the adrenal function without losing the control of the disease.

Material and methods: In 5 patients with difficult, uncontrolled asthma despite treatment with OCS, inhaled and systemic glucocorticosteroids were replaced with very high doses of ciclesonide (1600–2400 µg/day). The symptoms of asthma and the lung function were assessed at baseline and on the 28th, 56th and 70th day of treatment, whereas the levels of cortisol and adrenocorticotrophic hormone (ACTH) in the morning were measured at baseline and on the 28th and the 56th day of treatment.

Results: In all patients, the control of asthma symptoms, measured with Asthma Control Test questionnaire, improved from the mean score of 9.4 to 19.8 in 70 days. In 4 subjects force expiratory volume in 1 s improved gradually through the entire study reaching a mean improvement of 585 ml in 70 days. The ACTH levels were normalized in 3 patients after 28 days of observation and in all patients after 56 days. The cortisol level was normalized in 4 patients after 28 days and in another subject after 56 days of treatment with ciclesonide.

Conclusions: Switching from prednisone to very high doses of ciclesonide normalized the hypothalamic-pituitary-adrenal axis function and also improved the disease control and the lung function in these 5 patients with difficult asthma.

Key words: ciclesonide, corticosteroids, severe asthma, therapy, adrenal function.

Introduction

The treatment of chronic airway inflammation in asthma requires a systematic and continuous anti-inflammatory therapy. Inhaled corticosteroids (ICS) are the most effective class of drugs, which suppress inflammation and alleviate the symptoms of the disease [1]. Not surprisingly, ICS are recommended as the first-line therapy of asthma treatment, regardless of the type of the disease and the patients' age [2].

The safety of ICS depends on their dose, formulation and pharmacological properties. It has been accepted that in adults a safe daily dose of ICS, which does not increase the risk of significant side effects, is equivalent to 400 µg of budesonide [2]. Therefore, while the use of low to moderate doses of ICS is not associated with

a substantial risk of systemic side effects, such a risk becomes significant in patients requiring high doses. Several attempts have been made to minimize the dose of ICS without losing their efficacy. The introduction of hydrofluoroalkanes (HFAs), as carrier-solvents, and so-called "extra-fine" preparations containing a high proportion of respirable fraction of particles in metered dose inhalers (MDI) improved significantly ICS deposition in the lungs [3–5]. This also resulted in the reduction of local side effects, such as oral candidiasis and dysphonia, however, did not eliminate completely their systemic impact. Currently used ICS differ in this respect, especially in relation to the suppression of adrenal glands. The effect of hypothalamic-pituitary-adrenal (HPA)-axis suppression has been demonstrated for the majority of currently used ICS [6–13]. Interestingly, it has been shown

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that the degree of HPA suppression is different for the same inhaled corticosteroid and depends on its formulation [14]. Fluticasone (FP) administered with a dry power inhaler (DPI) did not differ from placebo in this respect, while the same dose of FP in chlorofluorocarbon (CFC) formulation in MDI significantly decreased the concentration of plasma cortisol [14]. These observations indicate that the systemic side effect depends more on the dose deposited in the lung than the labeled dose. When compared to other ICS, ciclesonide (CIC) seems to be the closest to the “ideal inhaled steroid”. The CIC is a product of a modern philosophy in drug manufacturing, which was designed as a prodrug with high lung deposition (up to 52%), high relative-glucocorticoid-receptor-binding affinity (RRA = 1200) and very high plasma protein binding (approximately 99%) of its active metabolite (desisobutyl-ciclesonide, des-CIC) [15]. Furthermore, CIC is close to an ideal due to its low risk of local and systemic side-effects, low bioavailability, extensive first-pass metabolism and wide therapeutic dose range. It has been proved that CIC both in moderate (320 µg/day) [15] and high doses (640 µg/day [16] or 800–1600 µg/day [17]) had no effect on HPA-axis suppression. Although 640 µg/day is the highest approved dose for CIC, sometimes significantly higher doses of CIC (reaching 1600–2400 µg/day) are used in clinical practice. However, the effect of such a therapy on adrenal suppression has been poorly investigated.

Material and methods

Study design

This was an open-label, one-center study involving 5 volunteers. All participants signed informed consent

and the study was approved by the Ethical Committee of the Medical University in Lodz. All patients reported at least a 20-year history of asthma defined as uncontrolled and difficult to treat, as specified in asthma management guidelines [2]. At baseline, the treatment (apart from other medications) included prednisone in the mean dose of 15 mg/day taken continuously and inhaled corticosteroids in high doses, equivalent to 800–1600 µg of budesonide. The patients' baseline characteristics are presented in Table 1. The exclusion criteria comprised well-controlled asthma, known or suspected hypersensitivity to CIC, active malignancies, inability to understand procedures associated with the study or to perform spirometry or to inhale CIC properly, active tuberculosis, asthma exacerbation 4 weeks preceding the study, necessity of taking systemic corticosteroids due to the exacerbation of asthma during the study or due to diseases other than asthma.

The medical history was taken and physical examination was performed in all patients at baseline. Asthma control was assessed by means of the asthma control test questionnaire and spirometry was performed in all participants. The blood sample for ACTH and cortisol levels was taken in the morning before 8:00 am. After the assessment of inclusion and exclusion criteria, currently used ICS were withdrawn and the patients started treatment with inhaled CIC. It was an add-on treatment option, with a daily dose ranging 1600–2400 µg/day (from 5 puffs twice a day to 5 puffs 3 times a day). The patients continued treatment with inhaled CIC and with previously used medicaments whereas the dose of prednisone was gradually decreased according to an individualized plan, which was designated to achieve and maintain asthma control. Furthermore, physical examination,

Table 1. Patients' characteristics

Parameter	Patients				
	EP	LW	ZB	KS	TZ
Age [years]	61	47	58	34	42
Sex	F	F	M	F	M
Duration of asthma	30	30	35	30	22
Allergy	D.pt, D.far, flour, grass, birch	D.pt, D.far, cat	None	D.pt, D.far	D. pt, D.far, grass
Steroids bursts/year	4	7	Constantly	5	6
Dose of prednisone at baseline	30	20	10	10	5
Recommended dose of ciclesonide [µg/day]	2400	2400	1600	1600	1600
Asthma treatment (daily dose)	Salmeterol (100 µg) Singulair (10 mg)	Formoterol (18 µg) Singulair (10 mg)	Formoterol (18 µg) Singulair (10 mg)	Formoterol (18 µg) Singulair (10 mg)	Formoterol (18 µg) Singulair (10 mg)
Smoking history	No	No	Yes	No	No
Comorbidities	Atopic dermatitis, allergic rhinitis, diabetes mellitus	Allergic rhinitis		Allergic rhinitis	Allergic rhinitis

D.pt – *Dermatophagoides pteronyssinus*, *D.far* – *Dermatophagoides farinae*, *COPD* – chronic obstructive pulmonary disease

ACT and spirometry were performed on the 7th, 28th, 56th and 70th day of treatment whereas blood sampling for ACTH and cortisol levels was performed in the morning on the 28th and 56th day of treatment with CIC.

Spirometry

Spirometry was performed with a daily calibrated spirometer (Lung Test 1000, MES Dymek, Dabrowski SA, Krakow, Poland), according to the ERS/ATS guideline [18]. The values of force expiratory volume in 1 s (FEV₁) and forced expiratory volume were expressed in liters and as the percentage of predicted values.

Asthma control test

The Asthma Control Test (ACT) was used for the assessment of the disease control level, according to the recommendations [19]. The maximum score was 25 and asthma was considered as not well controlled if the result of ACT was < 19 points.

Determination of adrenocorticotrophic hormone and cortisol levels in the serum

Serum cortisol and ACTH levels were measured with standardized, commercially available tests (Vitros Cortisol Reagent Pack by Ortho-Clinical Diagnostics, Cardiff, UK, and ACTH Test for Siemens Medical IMMULTE 1000) by Siemens Healthcare Diagnostics (Inc., Tarrytown, NY, USA). Normal plasma ACTH concentration is 10–60 ng/l

whereas for cortisol normal concentration at 8:00 is 138–635 nmol/l. The sensitivity of these assays is 3 nmol/l.

Administration of ciclesonide

Commercially available CIC was prescribed in the dose 160 µg/puff (Alvesco, Nycomed, Zurich, Switzerland) and was inhaled at a daily dose from 1600 µg (5 puffs twice a day) to 2400 µg (5 puffs three times a day) (Table 1).

All patients were instructed how to inhale the medication properly and the method of CIC inhalation was assessed by physicians at each visit during the study.

Results

The evaluation was conducted in 5 patients (3 women and 2 men) with poorly controlled asthma who were treated in an outpatient clinic of our hospital (Table 1). The discontinuation of prednisone was achieved after 3 days in patient TZ, 6 days in ZB and KS, and 10 days in EP and LW patients.

Morning baseline ACTH levels were below the lower limit of normal values in 4 patients (Figure 1 A, prednisone), whereas the cortisol concentration was below the lower range in 3 subjects and in 2 patients was normal, however close to the lower limit of its morning concentration in blood (Figure 1 B, prednisone).

The ACTH levels were normalized in 3 patients after 4 weeks and in all subjects after 56 days of CIC intake. Cortisol levels were normalized in 4 patients after 4 weeks of treatment (28th day). After another 4 weeks, in the

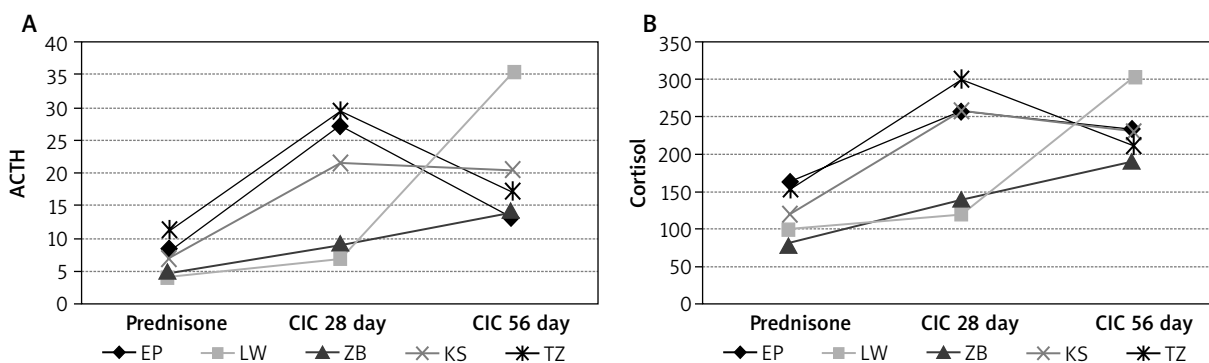


Figure 1. Serum levels of ACTH (A) and cortisol (B)

Table 2. Plasma concentrations of adrenocorticotrophic hormone (ACTH) and cortisol, force expiratory volume in 1 s (FEV₁) and ACT score

Parameter	Baseline	7 day	28 day	56 day	70 day
ACTH [nmol/l]	7.08 ±2.63	–	18.88 ±10.3	20.02 ±9.02	–
Cortisol [nmol/l]	123.6 ±34.8	–	215.0 ±79.8	233.8 ±42.0	–
FEV ₁ [l]	1.78 ±0.39	1.9 ±0.57	2.12 ±0.66	2.19 ±0.62	2.23 ±0.69
ACT [pt]	9.4 ±0.89	–	18.4 ±3.78	20.4 ±3.05	19.8 ±2.77

Values are presented as mean with standard deviation

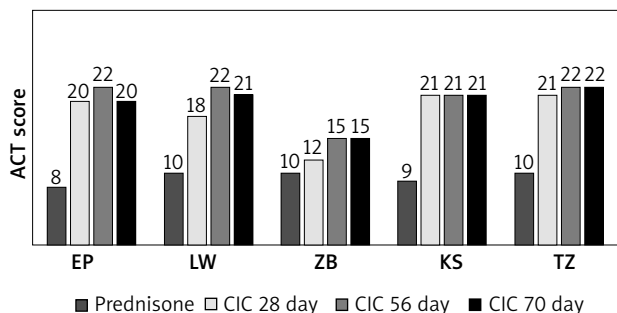


Figure 2. ACT score in patients treated with ciclesonide

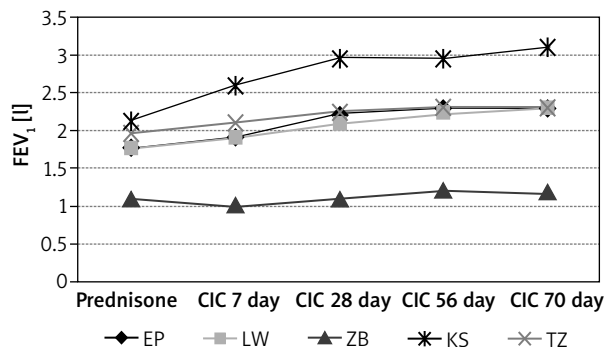


Figure 3. Force expiratory volume in 1 s (FEV₁) in patients treated with prednisone (baseline) and ciclesonide (CIC)

last patient, cortisol levels increased and after 56 days of therapy, in all patients, the cortisol level was normal (Figure 1 B, Table 2).

All patients showed improvement in asthma control at all time points of observation expressed in ACT scores from the mean value 9.4 pt at baseline to 18.4, 20.4, 19.8 at 4, 8 and 10 weeks of CIC treatment (Figure 2). In 4 patients, the mean FEV₁ increased from 1.91 l at baseline by 217.5 ml, 465 ml, 527 ml and 585 ml after 7, 28, 56 and 70 days of treatment, respectively (Table 2). Only in 1 patient, with very severe obstruction at baseline, no difference in FEV₁ value was observed (1.1 l at baseline to 1.17 l after 10 weeks of treatment with CIC) (Figure 3, Table 2).

Discussion

In this study we have demonstrated that oral corticosteroids, used at baseline by the patients with uncontrolled asthma, may be replaced by very high doses of CIC, which improves disease control and reverses adrenal suppression secondary to the use of prednisone.

Inhaled corticosteroids remain the most important anti-inflammatory form of asthma treatment. Although all of them are effective, there are some differences between ICS in terms of their safety [20–22]. The ICS are approved and considered as safe in the treatment of pregnant patients [23, 24]. However, Blais reports the possibility of an increased risk of congenital malformations in mothers treated with > 1000 µg of BDP [25].

In severe asthma, the addition of long-acting β₂ agonist (LABA) to therapy with a moderate dose of ICS seems to be more effective than a sole increase in the ICS dose [25, 26]. This thesis, however, has never been examined with CIC. Moreover, in severe asthma, systemic ICS are considered as the only alternative form of treatment to a high dose of ICS. However, a substantial risk of systemic side effects limits their wide application [27].

Ciclesonide is approved for the treatment of asthma in a very vast range of doses [22, 28, 29]. A major advantage of CIC is a wide margin of therapeutic range and high safety profile at high doses. Our observations have

shown that CIC at a dose of 1600–2400 µg/day improved asthma control, expressed by ACT scores, improved FEV₁ in the majority of patients as well as normalized the ACTH and cortisol levels in all patients. Previous observations indicated the absence of systemic effects of CIC at doses of up to 640–1280 µg/day [15]. The idea of using higher doses of CIC seems to be very promising. Szeffler *et al.* reported significantly reduced serum cortisol AUC 0–24 h after 1780 µg/day of fluticasone in contrast to an unchanged level at a dose of 1280 µg/day of CIC [30]. Heller *et al.* [31] observed the reversal of adrenal suppression caused by high doses of inhaled fluticasone in 4 children with asthma treated with high doses of CIC. These observations reinforce the strength of arguments that CIC should be designated for severe asthma requiring high doses of ICS.

In our study all patients were able to discontinue oral corticosteroids permanently (OCS) during the whole 10 weeks of observation. Bateman revealed a similar effect using a dose of 640–1280 µg in a group of 141 patients with steroid-dependent asthma yielding a 30% rate of permanent discontinuation of OCS [32]. It is worth stressing that the improvement of asthma control was achieved in all patients, regardless of the phenotype of the disease, both with a history of atopy, poor reversibility (TZ) or smoking history (ZB). The lack of noticeable improvement of FEV₁ in ZB patient may result from smoking reported by this patient and probably more pronounced COPD phenotype.

In the assessment of HPA axis we did not use the method recommended by the Asthma Clinical Research Network based on the analysis of an overnight in-laboratory evaluation of plasma cortisol every hour or every 2 h. In our study, we applied a simple single measurement of morning cortisol, which may be beneficial due to the practical character of the study [13].

An interesting fact concerning our study was that the beneficial effect of prednisone withdrawal was observed especially in patient TZ, who was taking a minimal dose of prednisone (5 mg/day) at baseline. This phenomenon is difficult to explain, but proves that the use of even

small repeated doses of OCS leads to an impaired HPA axis, which is reversible after switching to CIC [33].

Conclusions

Oral corticosteroids are currently used as the last-line therapy of difficult asthma, if previously recommended steps of treatment are not effective enough to control the disease, but may produce substantial systemic side effects and suppress the HPA axis. Very high doses of inhaled CIC do not produce significant side effects and may improve the lung function and disease control. Switching from OC to very high doses of CIC may also be beneficial in reversing the adrenal suppression caused by OC. Therefore, it is worth continuing studies which would state if very high doses of CIC could be regarded as a treatment option for patients with difficult asthma, who are considered as candidates for OC.

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Conflict of interest

All authors declare no conflict of interest.

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