SHORT COMMUNICATION

Drug Safety 2008; 31 (9): 769-774
0114-5916/08/0009-0769/$48.00/0

Inhaled Corticosteroids and Adrenal Insufficiency

Prevalence and Clinical Presentation

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Abstract

Objective: Adrenal insufficiency (AI) is a potentially life-threatening condition. It is known that high doses of inhaled corticosteroids (ICS) can induce systemic adverse effects. Currently, there are no data on the prevalence of AI associated with the use of ICS. This study aimed to investigate the prevalence and clinical presentation of AI (associated or not associated with exogenous Cushing's syndrome) in patients who were prescribed ICS by French physicians during the period 2000–5.

Methods: All metropolitan French paediatricians, endocrinologists, pulmonologists and intensive care physicians (n = 11 783) were mailed questionnaires requesting information regarding cases of AI associated or not associated with exogenous Cushing's syndrome between 2000 and 2005. Data collected included patient demographics, oral corticosteroid or ICS used during the year preceding the diagnosis of AI, underlying condition(s), concomitant treatment(s), presenting clinical signs and symptoms, results of laboratory investigations and outcome. The French pharmacovigilance database was screened for spontaneous reports to determine the frequency of AI associated with the use of ICS, using the capture-recapture method.

Results: Forty-six cases of AI were identified. Twenty-three cases presented with clinical symptoms of AI alone and 23 with exogenous Cushing's syndrome. ICS prescribed were fluticasone propionate (n = 24), budesonide (n = 12) and beclometasone dipropionate (n = 5). In 82% (n = 32) of cases for which data were available, ICS were prescribed at high doses. A potential drug interaction was found in 12 cases. Thirteen cases of AI were identified in the French pharmacovigilance database, one of which was common with the questionnaire survey. The capture-recapture method provided an estimation of 598 (95% CI 551, 648) cases of AI associated with the use of ICS for the 2000–5 period in France.

Conclusion: The results of this study confirm the occurrence of adrenal insufficiency in patients treated with ICS. Although the prevalence of ICS-induced AI

reported in this study is low, the likelihood of under-diagnosis underlines the need to consider this risk in patients when prescribing these drugs.

Background

Evidence from case reports, systematic reviews and a meta-analysis of clinical trials have led to the conclusion that inhaled corticosteroids (ICS) may induce systemic effects at high doses.[1-7] Osteoporosis, iatrogenic Cushing's syndrome and adrenal insufficiency (AI) have been reported with ICS at dosages above 400–500 μg/day in children or 800–1000 μg/day in adults (beclometasone equivalent).[8,9] Using computerized records from general practice, Mortimer et al.[10] showed that the risk of AI associated with ICS was dose-related. However, the prevalence of AI in patients treated with ICS has not been estimated, and records of a diagnosis of AI in computerized datasets remain speculative with no clinical or biological validation. The present study investigated the prevalence and clinical presentation of AI in patients who were prescribed ICS by French physicians, during the period 2000–5.

Methods

Data Collection

A total of 11 783 French paediatricians, endocrinologists, pulmonologists and intensive care physicians (including paediatric endocrinologists) were contacted by mail in March 2005. They were asked to report all cases of AI or Cushing's syndrome they had observed among children (<15 years) and adults (≥15 years) who were prescribed ICS between the years 2000 and 2005; the legal cut-off age in France was used to define a child and an adult. Inclusion criteria included treatment with ICS for at least 1 month and the occurrence of symptoms of AI during treatment or within 3 months after drug withdrawal. Patients received no systemic corticosteroid therapy during the 3 months preceding the diagnosis of AI.

Physicians received two questionnaires. The first questionnaire collected data regarding the patient's age, sex, diagnosis, date of diagnosis and information on any oral corticosteroid and ICS used during the year preceding the diagnosis of AI. For each reported case of AI or Cushing's syndrome, a second questionnaire was sent out to collect details on co-morbid conditions, concomitant medications used in the year preceding the diagnosis, clinical sign(s) including clinical features of exogenous Cushing's syndrome, results of laboratory investigations (plasma sodium, potassium and glucose levels, serum levels of dehydroepiandrosterone sulphate, 8:00 am plasma ACTH [corticotrophin] and cortisol concentrations, 24-hour urinary free cortisol and peak plasma cortisol levels after stimulation tests [standard, low-dose ACTH test or insulin intolerance test]).

All cases were validated by an expert committee that included adult and paediatric pulmonologists and an endocrinologist. Cases with another possible cause for AI were excluded. A diagnosis of ICS-induced AI was confirmed in patients who showed at least one of the following abnormalities: 8:00 am plasma cortisol or 24-hour urinary free cortisol below the normal range (8:00 am plasma cortisol = 200–700 nmol/mL, 24-hour urinary free cortisol = 80–270 nmol/24h); a peak plasma cortisol concentration below 550 nmol/L after a standard, low-dose short ACTH test or insulin tolerance test.[11] Concomitantly, the French pharmacovigilance database was screened for all reported cases of AI associated with the use of ICS that corresponded with our inclusion criteria for the period 2000–5.

Data Analysis

Qualitative data are given as a number and percentage, and quantitative data as a mean, SD and range. Statistical analyses were performed using the SAS® version 9.2 software (SAS Institute, Cary, NC, USA).

The capture-recapture method was used to provide population estimates from two or more incomplete sources of information. Physician responses to

questionnaires related to AI in patients treated with ICS and data from the French pharmacovigilance system allowed the use of the capture-recapture method to estimate the total number of cases of AI that occurred between 2000 and 2005, using the standard formula:[12,13]

$$N = \frac{(n_S \times n_{pv})}{(n_{S+pv})}$$

where N is the total estimated number of cases, n_s is the number of cases reported in the present study, n_{pv} is the number of cases reported to the pharmacovigilance system, and n_{s+pv} is the number of cases reported both in the present study and the pharmacovigilance system.

The protocol of the study was approved by the French national data-protection commission (Commission Nationale de l'Informatique et des Libertés [CNIL]) in charge of authorizing data processing.

Results

Fifty-two physicians (19 endocrinologists, 16 paediatricians, 13 pulmonologists and 4 intensive care physicians) reported 70 cases of AI; the expert committee validated 46/70 cases based on the clinical and laboratory data provided. Twenty-four cases were excluded from further analysis: an ICS was not used in 5 cases, 7 patients were treated with systemic corticosteroids, and in 12, AI occurred outside the limits of the study period. The most frequent underlying disease for which ICS was prescribed was asthma (50%) or 'another disease' (28%), which included cystic fibrosis, chronic obstructive pulmonary disease, pulmonary dysplasia and pulmonary fibrosis.

Of the 46 patients presenting with AI, 23 (50%) had clinical signs of exogenous Cushing's syndrome. Clinical presentations were not reported for 8 of the 23 remaining patients with AI without Cushing's syndrome. Reported clinical characteristics for children and adults are detailed in table I.

Treatments

The ICS most frequently prescribed for children were fluticasone propionate (n = 7), budesonide (n = 5) and beclometasone dipropionate (n = 2). In all but three cases, the mean daily dose of ICS was >500 μg beclometasone equivalent (i.e. budesonide >400 μg/day and fluticasone >250 μg/day). In the remaining three cases, the mean daily dose was 500 μg beclometasone equivalent.

The ICS commonly prescribed for adults were fluticasone (n = 16), budesonide (n = 7) and beclometasone (n = 2). Data regarding dosage were not provided for one adult treated with budesonide and four adults treated with fluticasone. In all but four cases, the mean daily dose of ICS was greater than 1000 μg/day beclometasone equivalent (i.e. budesonide 800 μg/day, fluticasone 500 μg/day) [table II].

Exposure to intranasal corticosteroids was reported in two cases. The first patient was a female, with no record of age, who was treated with 4000 μg

Table I. Clinical characteristics and demographics of patients with adrenal insufficiency with or without Cushing's syndrome

Characteristic	Children (n = 14)	Adults (n = 30)
Age [median (range) y]	9.5 (0.3–14)	45.5 (16.0–82.0)
Sex ratio (F/M)	1.0	1.9
Patients with no reported clinical signs [n (%)][a]	0 (0)	6 (20.0)
Declared clinical symptoms (n)[b]		
AI		
anorexia	1	5
weight loss	1	3
hypotension	0	3
coma	0	2
malaise	0	2
abdominal disorders	0	1
other AI-related symptoms (e.g. asthenia)	1	5
Cushing's syndrome		
facial rounding with plethora	7	9
unexplained weight gain	4	5
facial erythrosis	2	6
proximal myopathy	2	4
growth retardation	6	0
hypertension	2	3

a No age specified for two patients.

b More than one was possible.

AI = adrenal insufficiency; **F** = female; **M** = male.

Table II. Mean daily dosage (μg/day) of inhaled corticosteroids (ICS) in children and adults with adrenal insufficiency

ICS	Children[a] (n = 14)	Adults[b] (n = 30)	Age not specified
Fluticasone [no. pts. (no. w/o dose data)]	7 (0)	20 (4)	1 (0)
mean dosage (SD)[c]	785.7 (303.7)	1562.5 (478.7)	2000.0
dosage range[c]	250.0–1000.0	1000.0–2000.0	2000.0–2000.0
Budesonide [no. pts. (no. w/o dose data)]	5 (0)	8 (1)	
mean dosage (SD)[c]	1180.0 (782.3)	1211.4 (566.5)	
dosage range[c]	400.0–2000.0	400.0–2000.0	
Beclometasone [no. pts. (no. w/o dose data)]	2 (0)	2 (0)	1 (0)
mean dosage (SD)[c]	625.0 (176.8)	1150.0 (495.0)	2000.0
dosage range[c]	500.0–750.0	800.0–1500.0	2000.0–2000.0

a Children: aged <15 years.

b Adults: aged ≥15 years.

c Patients with data on drug dosage.

pts = patients; **w/o** = without.

(beclometasone equivalent) of inhaled fluticasone and 110 μg of intranasal triamcinolone acetonide. The second patient was an adult male treated with beclometasone 800 μg and who received 2 months' supply of intranasal fluticasone at a daily dose of 200 μg. Potential drug interactions were suspected in 12 cases with concomitant use of fluticasone and ritonavir (n = 6), fluticasone and itraconazole (n = 4) and budesonide and itraconazole (n = 2).

Estimation of Frequency

The French pharmacovigilance database had on record 16 cases of AI related to ICS use during the period 2000–5; three of these cases were excluded because of the use of systemic corticosteroids during the month preceding the diagnosis. Of the 13 remaining cases, 7 had Cushing's syndrome and 6 AI only. The questionnaire survey and the pharmacovigilance database had only a single case of Cushing's syndrome in common. According to the capture-recapture method, the number of cases of AI with ICS was estimated at 598 over the 5-year study period (95% Poisson CI 551, 648).

Discussion

The present study is a first estimation of frequency and clinical presentation of iatrogenic AI in the population of patients treated with ICS in France. There were 598 cases (95% Poisson CI 551, 648) of AI documented during the period of 2000–5 in France for 10 million units/year of ICS sold.[14] This study suggests that the frequency of AI related to the use of ICS is relatively low in France; one has to consider this in respect of the prevalence of primary AI estimated at 39–60 cases per million persons.[15] Our estimation is not based on a defined patient population as we had no valid method at our disposal to distinguish patients treated with standard and high doses of ICS. The only accurate data related to sales of ICS in France.

It should be emphasized that under-reporting of AI was likely by the 11 783 physicians who were mailed questionnaires. This is also true for the pharmacovigilance system in France where the magnitude of under-reporting of adverse drug reactions has been estimated to be about 95%.[16] The capture-recapture method is specifically designed for these situations of incomplete data collection, and minimizes the impact of under-reporting of diagnosed cases. In this study, the prevalence of AI was calculated on the basis of diagnosed cases. It is well known that the diagnosis of isolated AI is difficult and delayed due to the non-specificity of the presenting symptoms.[11] The death of Emma Agnes Frame, in Scotland, UK, whose AI was not diagnosed until 3 months after her death, served to illustrate the difficulty of diagnosing isolated cases of AI.[17] Furthermore, our questionnaire was sent to specialist physicians only and therefore did not take into account cases of AI identified by general practi-

tioners. We hypothesized that this would be an unlikely event. However, if that is indeed the case, then the reported prevalence is low. Thus both under-diagnosis and potential non-referral of some cases to a specialist physician could have underestimated the frequency of AI related to the use of ICS in this study.

The risk of ICS-induced AI has been reported to be dose-dependent.[10,18] Accordingly, in this study, almost all patients with AI were prescribed high doses of ICS, regardless of the presence or absence of Cushing's syndrome. Sixty-one of seventy cases with potential AI were prescribed fluticasone. This may be due to the fact that fluticasone is twice as potent as other ICS [19] and should be prescribed at half the dose of beclometasone, a caution that may not be familiar to prescribers. Similar findings were reported by Todd et al.;[20] however, differences in study design make comparisons difficult.

In two cases, intranasal corticosteroid use was reported. One patient was exposed to <1000 μg beclometasone, but also received a short course (2 months) of intranasal fluticasone 200 μg/day. This additional exposure may have been sufficient to potentiate AI precipitated by inhaled ICS.[21] In the second patient, AI was likely to be caused by exposure to a very high dose of fluticasone (4000 μg). These cases highlight the need to consider potential adverse effects with cumulative corticosteroid exposure and were included in the estimation of frequency. In patients with suspected drug interactions and treated with concomitant ritonavir and itraconazole, increased plasma corticosteroid levels due to inhibition of drug metabolizing enzymes may have led to AI. This concerns, in particular, the inhibition of the cytochrome P450 3A4 enzyme; thus prescribing an ICS concomitantly with an inhibitor of this enzyme should be avoided. Where necessary, patients should be monitored and the minimal effective dose of ICS sought for. In this respect, beclometasone seems to be a safer option.[22]

Conclusion

AI induced by ICS exists and probably at a higher frequency than currently thought. Our data confirms that this event mainly occurs at dosages of ICS over 500 μg/day beclometasone equivalent in children and 1000 μg/day beclometasone equivalent in adults and in patients taking enzymatic inhibitors. As suggested by Paton et al.[23] and the Global Initiative for Asthma (GINA) guidelines,[24] patients should be prescribed the minimal effective dose of ICS. When the patient's condition requires a high dose of ICS, his or her adrenal function should be monitored ideally with the use of the short Synacthen test. In the case of secondary AI, patients should be provided with information regarding acute adrenal crises, conditions of occurrence, clinical symptoms and prevention.

Acknowledgements

This study was supported by an unconditional grant from Merck & Co. who had no role in the study design, the collection, analysis and interpretation of data, the writing of the report or the decision to submit the paper for publication. We thank Abdelilah Abouelfath for assistance in statistical analysis and Fanny Depont for project management, and Guillaume Hébert and Philip Robinson for help in manuscript preparation. The authors declare no conflicts of interest.

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