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PHARMACODYNAMICS

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Reported adverse drug reactions during the use of inhaled steroids in children with asthma in the Netherlands

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Abstract *Objectives:* Inhaled corticosteroids (ICS) are widely used in the treatment of asthma. We studied the suspected adverse drug reactions (sADRs) reported during the use of ICS in the Netherlands. *Methods:* In the Netherlands, health professionals and patients can report suspected ADRs to the Pharmacovigilance Centre Lareb. All reported sADRs on ICS were categorised and assessed as to whether these were likely to be associated with use of the steroid. Age and gender adjusted Reported Odds Ratios (RORs) and Naranjo Scores (NS) were computed for sADRs reported more than 3 times. *Results:* Since 1984, sADRs of ICS were reported in 89 children (mean age 6 years), 48 (54%) were boys. Suspected drugs were fluticasone in 46 children (52%), budesonide in 21 (24%), and beclomethasone in 22 cases (24%). Psychiatric symptoms were reported in 19 children (21%; ROR 3.8, NS 3.6), growth retardation in 6 children (7%; ROR 47.8, NS 3.0) and rashes in 6 cases (7%; ROR 0.7, NS 2.4). There were 7 reports (8%; ROR 2.1, NS 3.4) concerning abnormalities of the teeth, 4 reports of alopecia (4%; ROR 3.3, NS 3.5), and 3 reports of hirsutism and hypertrichosis (NS 4.0). Non-fatal adrenal insufficiency was reported once. *Conclusions:* Alteration of behaviour was the most frequently reported sADR. There are more indications that alterations of behaviour could be a real sADR of ICS. Non-fatal adrenal insufficiency was the only reported possible life threatening sADR. The association of hypertrichosis and teeth abnormalities after ICS in children has not been reported in the literature before.

Keywords Inhaled corticosteroids · Naranjo scores · Reported odds ratios · Suspected adverse drug reactions

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Introduction

Inhaled corticosteroids (ICS) are the mainstays in the treatment of asthma in both children and adults. Several guidelines advise the early introduction of ICS in maintenance treatment of persistent asthma [2, 3, 11]. However, as in every category of drugs, adverse drug reactions may occur. Well-known adverse drug reactions after ICS in children include growth retardation, adrenal suppression, hoarseness, oral candidiasis, and laryngeal irritation [16]. These are included in the Summary of Product Characteristics.

Other less prevalent adverse effects have been recognised and are included in reference textbooks and sources such as Meyler's Side Effects of Drugs and Micromedex [4, 5].

To broaden the knowledge of ADRs after ICS in children we studied the reports of suspected adverse drug reactions (sADRs) in the Netherlands. We wanted to know which sADRs were reported the most frequently. Furthermore, we were interested to find reports of new sADRs and whether life-threatening sADRs were reported.

Methods

For this study, we used the database of the Dutch Pharmacovigilance Centre Lareb. Health professionals and, since 2004, patients or caregivers can report sADRs to Lareb, which collects and analyses sADRs, voluntarily reported, on behalf of the Dutch Medicines Evaluation Board.

Reports include at least the ADR observed, drug involved, age, and sex of the patient. Reports that are received are subject to review by qualified assessors. Data concerning the suspected adverse drug reaction and the drugs involved are coded using the Medical Dictionary for Regulatory Activities http://www.meddramsso.com/NewWeb2003/index.htm, MedDRA) adverse drug reaction terminology and the anatomical therapeutical chemical (ATC) classification drug coding system respectively, and subsequently filed in a database. This database was searched for reported sADRs by ICS in children younger than 17 years of age.

Computations

The relationship between ICS and reported sADRs were evaluated mathematically by computing the Reporting Odds Ratios (RORs) and de Naranjo Scores (NSs). The ROR compares the frequency of the reported sADR for a certain drug with the frequency of reports of that adverse effect for all other drugs in the Pharmacovigilance database. A statistically significant ROR might be an indication for a possible causal relationship between the drug and the reported complaints. The RORs and 95%-confidence intervals (95%CI) were calculated in a case/non-case design [21]. RORs adjusted for age and gender were calculated by means of logistic regression analysis.

Another way to get an impression of the probability of a causal relationship is the Naranjo Score (NS). The NS evaluates the causality of drugs on an individual basis [22]. The NS varies from 0, indicating no association, to 10, indicating a proven causal association. Originally, the NS was developed for evaluation of sADRs in hospitalised patients. Because in outpatients the evaluation of sADRs is limited, the NS of sADRs in outpatients is generally lower than in hospitalised patients. A NS from 1 to 4 is considered to reflect a possible association in outpatients. Both the ROR and NS were computed when a sADR was reported at least 4 times. For computations and statistical analysis we used SPSS (version 11.0).

Results

In the period of June 1984–October 2004, Lareb received 46,314 reports of sADRs. Of these, 2,499 reports (5.4%) concerned individuals younger than 17 years of age. In 89 of these 2,499 children (3.6%) one or more sADRs after ICS were reported. The median age of the children was 6 years and 48 (54%) of them were boys. Suspected drugs were fluticasone in 46 children (52%), budesonide in 21 (24%), beclomethasone in 19 cases (21%), and beclomethasone fine particles in 3 (3%).

Psychiatric symptoms, belonging to the system and organ class 'psychiatric symptoms' within the MedDRA classification system, were reported in 19 cases (21%). The symptoms included agitation and hyperactivity in 10 cases, aggression in 7 children and anxiety in 2. The ROR was 3.8 (95%C.I. 2.2–6.4), which is statistically significant. The mean NS was 3.6. We compared the group of children on whom a psychiatric sADR was reported with the group of children with other sADRs reported during the use of ICS. There were no gender differences, but the children on whom a psychiatric sADR was reported were statistically significantly younger (4.7 vs 6.6 years, p=0.01). Although the mean daily doses prescribed in the group of children with psychiatric symptoms was higher (318 µg vs 252 µg), this was not statistically significant. Only one patient received a dose higher than advised in the guidelines. This 6-year-old girl received a dose of 800 microgram budesonide daily via a pMDI and spacer. The drugs related to psychiatric symptoms did not differ from the distribution of the drugs associated with other sADRs.

Non-fatal adrenal suppression was reported in a 10-year-old girl, who received inhaled fluticasone (500 microgram daily) and nasal beclomethasone (100 µg daily).

There were a few sADRs never described before. Teeth discoloration and caries were reported in 7 children, the ROR was 2.1 (95%C.I. 1.0–4.8) and the NS was 3.4. Alopecia had been reported four times, the ROR was 4.2. Hirsutism and hypertrichosis were reported in 3 patients and the mean NS was 4.

Table 1 Numbers, crude and age and gender adjusted reporting odds ratios, and Naranjo scores of the suspected adverse drug reactions during the use of inhaled corticosteroids in children under 17 years of age, reported to the Dutch Pharmacovigilance Centre Lareb

ADRs	ADRs, associated with ICS	ADRs not associated with ICS	Crude ROR (95%C.I.)	Adjusted ROR (95%C.I.)	NS
Total	89	2410			
Psychiatric Symptoms	19	160	3.8 (2.2–6.5)	3.8 (2.2–6.4)*	3.6
Teeth abn.	7	95	2.1 (0.9–4.6)	2.1 (1.0–4.8)	3.4
Growth retardation	6	83	34.7 (10.4–116.2)	47.8 (11.7–176.1)*	3.0
Rash	6	83	0.7 (0.3–1.5)	0.7 (0.3–1.6)	2.4
Alopecia	4	34	3.3 (1.1–9.5)	4.2 (1.4–12.5)*	3.5
Headache	4	64	1.7 (0.6–4.9)	1.9 (0.7–5.3)	4.0

ADR = adverse drug reaction; ICS = inhaled corticosteroids, ROR = reporting odds ratio, NS = Naranjo score, 95%C.I.=95% confidence interval; abn. = abnormalities
*statistically significant

Growth retardation was reported in 6 patients. The ROR was 47.8 (95%C.I. 11.7–176.1) the NS was 3.0. Rashes were reported in 6 children, the ROR was 0.7, headache was reported 4 times, the ROR was 1.9, and both are not statistically significant. Table 1 summarises the sADRs, reported at least 4 times after ICS in children.

Other sADRs included: urticaria, cough, insomnia, epistaxis, facial oedema, excessive weight gain, abdominal pain, fatigue, diarrhoea, dyspnoea, eczema, hoarseness, bronchorrhea, bruising of the skin, amenorrhea, anorexia, cataract, gingivitis, mydriasis and pruritus.

Discussion

The efficacy of ICS in the treatment of persistent asthma is beyond any doubt [2, 3, 11]. However, like every drug they may cause ADRs. We were struck by the high frequency of reports of psychiatric alterations after ICS. The high NS and the adjusted ROR argue for a real association between psychiatric alterations after ICS in normal doses. As far as we know, the association between ICS and psychiatric sADRs has not studied extensively before.

It is well established that oral steroids can cause psychic alterations in adults and children [4]. Kayani compared oral courses of 1 mg/kg and 2 mg/kg prednisolone in asthmatic children and found significantly more anxiety, hyperactivity and aggressive behaviour in patients receiving the higher dose [15]. In 1988, a 9-year-old boy who exerted hyperactive behaviour after budesonide 200 micrograms daily was described [19]. More recently, Hederos described a group of 60 children of whom 9 (15%) experienced psychiatric side effects after high doses of budesonide [14]. Bender compared beclomethasone with theophylline, but found no differences [6]. However, they did not give absolute figures. Moreover, these children were 6–17 years old and most of the reports on psychiatric alterations in our study concerned children under the age of 5.

Elias exposed rats to inhaled budesonide and found a significant effect on learning and motivation functioning [10]. This is compatible with the concept that ICS "cross the borders between inhaled air and brain".

An alternative explanation of altered behaviour after ICS is that untreated asthmatic children could be hampered in their activity and therefore exert "hyperactivity" when their asthma is treated sufficiently. As far as we know, this has never been studied.

It is also possible that psychiatric alterations occur as a result of other concomitant medications. It is widely believed that beta-agonists lead to hyperactivity. Hajikoumi et al. [12] studied this in 19 pre-school children in a blinded crossover study, but did not find a difference between 5 mg salbutamol, administered via an oxygen driven nebuliser and placebo. However, they studied the effect of only one dose in children with or without asthma.

Finally, an alternative explanation could be that asthma by itself leads to behavioural problems. Indeed, in a recent study it was demonstrated that children who developed asthma had more behavioural problems than children who never wheezed [7]. Also, in a review McQuaid et al. [18] demonstrated that behavioural problems were more frequent in children with asthma than in controls. However, the high ROR and NS of the psychiatric symptoms argue for a real effect of ICS.

Taken together, we believe that one should be aware of a possible negative influence of ICS on psychiatric functioning of a child and that therefore a thorough study is warranted.

We did not find any reports of deaths after ICS treatment. A recent British study described two cases with fatal outcome in which ICS were involved [8]. Neither details of the mechanism of how the drugs contributed to the death of the children nor details were given. Therefore the role of ICS in these cases is difficult to assess.

Adrenal suppression is a potential life-threatening event and was reported only once during the study period in the Netherlands. It could be that adrenal suppression is not recognised and therefore is not reported. In a national survey in the United Kingdom of the occurrence of adrenal crises during ICS, 33 periods of adrenal crises in children from 3–10 years (mean 6 years) were identified. In 30 cases, fluticasone had been used and, in 27, at least one course of oral steroids had been used in the previous years. The doses of ICS were higher than generally recommended for children (mean daily dose 980 μg) [23]. Children receiving fluticasone in doses exceeding 400 μg daily and who have been treated recently with a course of oral steroids seem to be vulnerable.

There were some unexpected reported sADRs. Adverse effects on teeth (discoloration and caries) after ICS have not been reported before. Because discoloration of teeth has been described after the use of antibiotics, such as amoxicillin, and we do not have data on prior medication use, it could be that antibiotics might have played a role [20]. Although the NS is high, the relatively low ROR argues against an association. The relationship between sADR of ICS on teeth therefore remains unclear.

Hirsutism and hypertrichosis have never been reported to be associated with ICS in children before, although they are described after oral corticosteroids in adults [4]. The relatively high NS suggests a possible association.

Six reports to Lareb concerned a negative effect on growth. The high ROR and NS demonstrate the usefulness of these parameters. The effect of ICS on growth has been studied extensively. Although in children treated for years with ICS the final adult height did not differ from the expected height [1], we believe it is necessary to check the growth of children on ICS regularly.

Hoarseness was reported once to Lareb, whilst it was found in 14% of a French group of asthmatic children on ICS [9]. Although a frequency between 4 and 13% of oral candidiasis in patients on ICS is reported [13], Lareb did not receive any report concerning candidiasis.

Rashes were reported 6 times, but the ROR was not statistically significantly increased. As far as we know, the frequency of dermatological side effects in children has never been studied. In adults, negative effects on the skin have been well recognised. Mak [17] studied 202 asthmatic

adults on ICS and found that 47% of them had easy bruising versus 22% in a control group. Not surprisingly, risk factors were longer duration of treatment, older ages, and the use of higher doses of ICS. In children, these risk factors do not occur.

The frequency of other sADRs is too low for conclusions. The distribution of sADR and drugs involved does not differ from the distribution of prescription of individual ICS. In 2002, of 2,592 prescriptions for ICS in a representative Dutch population, 29% were for beclomethasone, 17% for budesonide and 54% for fluticasone (E. Schirm, personal communication).

A study like this has some limitations. First, in the Netherlands, reporting sADRs is voluntary, therefore not all sADRs, especially the better known ones, will be reported. This can lead to underreporting but this is inevitable in this kind of study. On the other hand, because of the voluntary nature of reporting, the persons who will report obviously have no other drive than being concerned about possible associations. Secondly, we used the NS to evaluate the association between the use of ICS and sADRs in outpatients. However, the NS is the only available measure for causality in outpatients. It should be kept in mind that neither the NS nor the ROR prove causality, but should merely be regarded as a sign of a possible association.

Based on the outcome of this study, we conclude that apparently there is an association between the use of ICS and behavioural changes in young children. Alteration of behaviour (agitation, hyperactivity) was the most frequently reported sADR of ICR in children. Adrenal insufficiency was the only reported potentially life-threatening sADR. The association with alopecia, hypertrichosis and hirsutism has not been described before and neither have dental abnormalities been reported.

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