Improving care in paediatric asthma
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Chapter 6: Reported adverse drug reactions during the use of inhaled steroids in children with asthma in the Netherlands.


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Abstract.

Introduction
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.
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.\textsuperscript{1,2,3} 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.\textsuperscript{4} 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.\textsuperscript{5,6}

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 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 Ratio's (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.\textsuperscript{7} 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. 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, 2499 reports (5.4%) concerned individuals younger than 17 years of age. In 89 of these 2499 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 ug vs. 252 ug); 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 microgram 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.
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 four times, the ROR was 1.9, and both are not statistically significant. Table 1 summarises the sADRs, reported at least four 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.

<table>
<thead>
<tr>
<th>ADRs</th>
<th>ADRs, associated with ICS</th>
<th>ADRs not associated with ICS</th>
<th>crude ROR (95%C.I.)</th>
<th>adjusted ROR (95%C.I.)</th>
<th>NS</th>
</tr>
</thead>
<tbody>
<tr>
<td>total</td>
<td>89</td>
<td>2410</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>psychiatric symptoms</td>
<td>19</td>
<td>160</td>
<td>3.8 (2.2 – 6.5)</td>
<td>3.8 (2.2-6.4)*</td>
<td>3.6</td>
</tr>
<tr>
<td>teeth</td>
<td>7</td>
<td>95</td>
<td>2.1 (0.9-4.6)</td>
<td>2.1 (1.0-4.8)</td>
<td>3.4</td>
</tr>
<tr>
<td>growth retardation</td>
<td>6</td>
<td>83</td>
<td>34.7 (10.4-116.2)</td>
<td>47.8 (11.7-176.1)*</td>
<td>3.0</td>
</tr>
<tr>
<td>rash</td>
<td>6</td>
<td>83</td>
<td>0.7 (0.3-1.5)</td>
<td>0.7 (0.3-1.6)</td>
<td>2.4</td>
</tr>
<tr>
<td>alopecia</td>
<td>4</td>
<td>34</td>
<td>3.3 (1.1-9.5)</td>
<td>4.2 (1.4-12.5)*</td>
<td>3.5</td>
</tr>
<tr>
<td>headache</td>
<td>4</td>
<td>64</td>
<td>1.7 (0.6-4.9)</td>
<td>1.9 (0.7-5.3)</td>
<td>4.0</td>
</tr>
</tbody>
</table>

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

Discussion

The efficacy of ICS in the treatment of persistent asthma is beyond any doubt. 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. 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.9 In 1988 a 9-year-old boy who exerted hyperactive behaviour after budesonide 200 micrograms daily
was described.\textsuperscript{10} More recently, Hederos described a group of 60 children of whom 9 (15\%) experienced psychiatric side effects after high doses of budesonide.\textsuperscript{11} Bender compared beclomethasone with theophylline, but found no differences.\textsuperscript{12} However they did not give absolute figures. Moreover, these children were 6 to 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.\textsuperscript{13} 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 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.\textsuperscript{14} 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.\textsuperscript{15} Also, in a review McQuaid et al demonstrated that behavioural problems were more frequent in children with asthma than in controls.\textsuperscript{16} 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 find any reports of deaths after ICS treatment. A recent British study described two cases with fatal outcome in which ICS were involved.\textsuperscript{17} 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 to the occurrence of adrenal crises during ICS 33 periods of adrenal crises in children from 3 – 10 years (mean 6 yr.) 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 microgram). Children receiving fluticasone in doses exceeding 400 micrograms 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 were not 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. 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. 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, 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. Although a frequency between 4 to 13% of oral candidiasis in patients on ICS is reported, Lareb did not receive any report concerning candidiasis.

Rashes were reported 6 times, 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 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 2592 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 merely should 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.

*We thank dr. J. Collins for reviewing the English.*
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Charlotte

This girl was referred to the outpatient clinic at the age of 10 years because of unstable asthma. She was hampered during sports and playing, woke up every night because of shortness of breath and used salbutamol daily. Fluticasone (100 µg twice daily), prescribed by her general practitioner did not have sufficient effect. Her growth was normal, and auscultation revealed wheezing. The skin prick test demonstrated sensitisation for dog, cat and horse. Spirometry revealed airway obstruction with good reversibility.

She was prescribed fluticasone/salmeterol 250/50 twice daily and the asthma nurse took care of her. This gave some, but not enough relief. Montelukast 5 mg daily was added. Since then, her asthma is stable and the fluticasone/salmeterol was tapered to 100/50 twice daily.

At the age of eleven increased growth of hair on arm, face and legs was noted. She reported that she was bullied because of this. Her growth had been normal and there were no signs of masculinisation. Laboratory studies revealed no hormonal abnormalities. After cosmetic treatment the dark hair became less visible. She was not bullied anymore, her asthma is stable.