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Hypertrichosis as a Side Effect of Inhaled Steroids in Children

T.W. de Vries, MD,[1]* J.J. de Langen-Wouterse, MPharmSc,[2] L.T.W. de Jong-Van den Berg, PhD,[3] and E.J. Duiverman, PhD[4]

Summary. Three spontaneous reports of patients in whom a relationship between hypertrichosis and inhaled corticosteroids (ICS) was suspected, were reported to Lareb, The Netherlands Pharmacovigilance Center. We sought evidence for and against a causal relationship between hypertrichosis and ICS in children. The relationship between hypertrichosis and ICS was studied mathematically by assessing the Reporting Odds Ratio (ROR) and by determining the Naranjo Score (NS). We also studied the reports sent to the Pharmacovigilance Database of the Uppsala Monitoring Centre (UMC) of the WHO and reviewed the literature. In the Dutch children, the ROR between hypertrichosis and ICS was 14.6 (95%CI 3.6–59.5), the NS was 4. In the database of the UMC 20 more reports on hypertrichosis and ICS were found, contributing to the results of the Dutch database. Taken together, 11 boys and 12 girls were involved with a mean age of 7 years (range 1–17). The time between the start of ICS and the occurrence of hypertrichosis varied between 1 month and 3 years. Besides the hypertrichosis, growth retardation was found in 5 children and adrenal suppression in 12. In 12 children the outcome after cessation was reported: in 6 children the hypertrichosis improved, whilst in 6 it did not. We found sufficient evidence to support the suspicion that hypertrichosis might be a true adverse effect of ICS. We found no simple dose-effect relationship but obviously there is an individual susceptibility. After cessation of ICS the exaggerated hair growth will not disappear in all children. Hypertrichosis may be a useful clinical pointer to exogenous steroid excess. **Pediatr Pulmonol. 2007; 42:370–373.**

Key words: asthma; inhaled corticosteroids; side effects; hypertrichosis; hair; individual susceptibility.

INTRODUCTION

Inhaled corticosteroids (ICS) are the cornerstones in the maintenance treatment of asthma.[1–3] Well-known adverse drug reactions of ICS include growth retardation, hoarseness, oral candidiasis, laryngeal irritation, and adrenal suppression.[4]

Recently we screened the reports of suspected adverse drug reactions (sADRs) in children associated with the use of ICS and found three reports on hypertrichosis.[5] In the present article we describe these patients in more detail. Also we describe the reports of the Pharmacovigilance Database of the Uppsala Monitoring Centre (UMC) of the World Health Organization (WHO) and discuss the plausibility of the relationship between ICS and hypertrichosis. In this article, hypertrichosis is defined as excessive hair growth, without a specific localization, whereas hirsutism is excessive hair growth in the masculine pattern.

REPORTS OF CASES IN THE DUTCH DATABASE

The first report concerns a 6-year-old girl who used 400 μg budesonide daily via a pressurized metered dose inhaler (pMDI) with a spacer. She had terbutaline as a reliever for acute dyspnoea. After the use of budesonide growth of hair on her back, arms and legs was noted.

The second report concerns a girl of 10 years who daily inhaled 500 μg fluticasone and budesonide 400 μg

[1]Department of Pediatrics, Medical Centre Leeuwarden, Leeuwarden, The Netherlands.

[2]Netherlands Pharmacovigilance Centre Lareb, 's-Hertogenbosch, The Netherlands.

[3]Department of Social Pharmacy, Pharmacoepidemiology and Pharmacotherapy, Groningen University Institute for Drug Exploration, Groningen, The Netherlands.

[4]Department of Pediatrics, Division of Pediatric Pulmonology, Beatrix Children's Hospital, Groningen, The Netherlands.

*Correspondence to: T.W. de Vries, MD, Department of Pediatrics, Medical Centre Leeuwarden, P.O. Box 888, 8901 BR Leeuwarden, The Netherlands. E-mail: tjalling.de.vries@znb.nl

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concurrently as well as 50 μg beclomethasone nasal spray. After 3 years hair growth on the back, arms and legs was noted. She also experienced non-fatal adrenal suppression and growth retardation, these were preceded by the hypertrichosis. From the reporting physician we learned that, after dose reduction of the ICS, the pattern of the hair growth normalized.

The third patient is a 3-year-old boy who inhaled fluticasone 250 μg daily for 3 months. He also had triamcinolone ointment for his skin. Growth of hair on his legs, arms and face was noted. We tried to contact the reporting physicians and pharmacists, only in the second case additional information was retrieved.

PHARMACOVIGILANCE DATA

Lareb, The Netherlands Pharmacovigilance Center, received 89 sADRs on ICS in children in the years 1984–2005, 3 of these concerned hypertrichosis (3.3%). The relationship between ICS and reported sADRs can be evaluated mathematically by computing the Reporting Odds Ratio (ROR). 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 database. A lower limit of the 95% confidence interval of above 1.0 suggests a possible relationship between the reported sADR and the suspect drug.[5] The ROR for hypertrichosis and ICS in the Dutch database is 14.6 (95%CI 3.6–59.5).

The Naranjo Score (NS) evaluates the causality of drugs on an individual basis. The NS includes relations between drugs and side effects in time, improvement after cessation of the drug, reappearance after reintroduction, exclusion of other causes of the adverse effect, and dose response relations.[6]

The mean NS of the three reports in the Dutch database for hypertrichosis and ICS is 4. Both the elevated ROR and NS are indicative of a possible causal relation between ICS and hypertrichosis.

We studied the database of UMC of the WHO for reports that might confirm the findings from the Dutch database. The database of the WHO comprised 3,230 reports on ICS and 105 of these subjects (3.2%) concerned hypertrichosis, which is nearly the same proportion as in the Dutch database. Twenty of these concerned individuals younger than the age of 19 years. Table 1 summarizes the reports of hypertrichosis in the 23 children of the UMC and the Dutch database.

Eleven boys and 12 girls were involved; their mean age was 7 years (range 1–17); 19 of them were younger than the age of 10. The drugs suspected include beclomethasone (three cases), betametasone (3), budesonide (10), fluticasone (6), and flunisolide (1). In two of the six children on fluticasone was the daily dose given. One of them, a girl, received 500 μg, this is more than 400 μg fluticasone which is considered the threshold for safety.[4] The other, a boy, received 250 μg fluticasone daily. The mean daily dose of the other steroids was 277 μg. The indication for use was asthma in eight children and allergic rhinitis in five, in the remaining cases the indications were not mentioned. One child also used itraconazol, a potent antifungal drug. It decreases steroid metabolism leading to higher systemic blood levels.[7] Other co-medications used were betamimetics. Twelve children used corticosteroids with more than one route of administration, for example, also for dermal use. Other drugs used include short and long acting betamimetics and oral antihistaminics.

TABLE 1— Summary of the 23 Reports of Hypertrichosis after ICS From the Vigibase and the Dutch Database

Sex (male/female)	11/12
Age	Mean 7 years (range 1–17 years)
Primary suspected drug	
Beclomethasone	3
Budesonide	10
Fluticasone	6
Betamethasone	3
Flunisolide	1
Daily dose	
Fluticasone	Mean: 375 μg (range 250–500 μg)
Other steroids	Mean: 277 μg (range 50–500 μg)
Indication[a]	
Asthma	8
Allergic rhinitis	5
Latency time[a]	Mean 9 months (range 1–36 months)
Outcome[a]	
Improved	6
Not improved	6
Other reported side effects[a]	
Growth retardation	5
Adrenal suppression	12

[a]Not mentioned in all cases.

The latency time between the start of using ICS and hypertrichosis in the UMC varied between 1 and 36 months. The follow-up after cessation of ICS was reported in 12 children, 6 improved and 6 did not. The duration of the follow-up had not been reported. Other side effects reported in these children were growth retardation in 6 patients and adrenal suppression and/or Cushing syndrome in 12 patients.

DISCUSSION

In The Netherlands, hypertrichosis was reported as a possible side effect of inhaled steroids. Because the Dutch Pharmacovigilance Center only receives reports of sADRs we do not have extensive information of the patients. We contacted the reporting physicians and pharmacists to get

additional information, and received some more information about the second case. The first patient had a dose of ICS, not exceeding the advised dose. The total dose of steroids in the second patient exceeded the maximum dose regarded to be safe.[4]

The third patient is a young boy on a normal dose of ICS but also using dermal steroids and itraconazole. The dermal use of triamcinolone could have increased the risk. However, in daily practice more children receive other forms of steroids during the use of ICS for allergic asthma often is accompanied by other conditions also treated with steroids, such as allergic rhinitis and atopic dermatitis.

The doses of ICS in two of these children were lower than the dose regarded to be safe, and in the reports the UMC in only one child did the dose exceed that level. This points more to an individual susceptibility than a dose-response relationship.

The latency between the start of the medication and the reported side effect in the reports varies from 1 month to 3 years. Here, however, must be kept in mind that it takes time for hair to grow and become visible, especially in Caucasian children. A possible relationship between the drug and the side-effect is therefore difficult to recognize.

Apparently, hypertrichosis can occur in girls and even in young children. The youngest child in which hypertrichosis was reported was 1 year of age.

In the literature, we found three descriptions of hypertrichosis in children connected to ICS. Hollman described an 8-year-old girl in whom inhaled triamcinolone caused not only growth retardation and obesity but also hypertrichosis. The hypothalamic-pituitary axis was tested and appeared normal. After cessation of the triamcinolone the symptoms, including the hypertrichosis, disappeared.[8] Patel reported eight children with adrenal insufficiency after ICS; in one of them, a 5-year-old boy, hypertrichosis was present. He had used budesonide 400 μg daily for 12 months. The follow-up of the hair growth was not described.[9]

Perry et al.[10] described nine children on intranasal steroids with signs of exogenous steroid excess and in five of these children also hypertrichosis was noted.

Thus, hypertrichosis was reported in combination with growth retardation and adrenal insufficiency in the literature as well as in the reports presented here.

Therefore, we believe that hypertrichosis is a sign of at an exogenous steroid excess and sometimes precedes adrenal insufficiency. After cessation of the ICS the hypertrichosis will improve in some children, as seen in the children of the UMC database, however, in other children it will not disappear. This could have an important impact on the social well-being of the children and especially the girls.

In the literature we found no reports of hypertrichosis in adults after ICS. Of course, hypertrichosis does not occur in male adults. The prevalence of hirsutism in the general adult female population is about 5%.[11] In a recent review, ICS were not mentioned as a possible explanation of hypertrichosis in adults.[12]

Hypertrichosis in childhood occurs rarely and has a wide differential diagnosis, including pubertas praecox, 21-hydroxylase deficiency, and excess of androgens in androgen producing tumors. Drugs associated with hypertrichosis are cyclosporine A, tacrolimus, phenytoin, and oral steroids. In oral corticosteroids such as dexamethasone and hydrocortisone, hypertrichosis is recognized as an infrequent side effect and is included in the Summary of Product Characteristics. Hypertrichosis occurs often in patients with endogenous excess of corticosteroids, such as Cushing's disease.[13] Although the systemic availability of inhaled steroids is far lower than that of oral steroids there is a wide variety in steroid sensitivity between individuals and in tissues.[4] It could be that some children are more susceptible than others are.

In conclusion, we believe that hypertrichosis is a rare but true adverse effect of ICS in children and that it is biologically plausible. The risk is possibly due to individual susceptibility and is increased after higher doses with concomitant steroid therapy for other diseases. Hypertrichosis may be a useful clinical pointer to exogenous steroid excess.

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