Lareb
Nederlands Bijwerkingen Centrum
Netherlands Pharmacovigilance Centre

Fluticasone inhalation and behavioural changes in children

Introduction

Fluticasone (Flixotide®) is an inhalation corticosteroid available on the Dutch market since 1994. It is registered for *the prophylactic treatment of asthma.* It is also indicated for *treatment of coughing and wheezing in asthmatic children aged one to four and for symptomatic treatment of moderate to severe COPD.*[1] Fluticasone is also available in combination with the long acting β_2-sympathicomimetic salmeterol under the name Seretide®.
The most common adverse drug reactions seen with the use of fluticasone are local reactions such as oral candidasis and hoarseness [1,2].

Reports

The database of the Netherlands Pharmacovigilance Centre Lareb contained 17 reports of behavioural changes in children (0-18 years) in association with the use of fluticasone or the combination fluticasone/salmeterol. In 11 cases the symptoms disappeared when fluticason was withdrawn. In case F, a positive rechallenge was observed.

Table 1. reports of behavioural changes associated with the use of fluticasone

Patient, Sex, age	Drug Indication for use	Concomitant medication	ADR	Time to onset, outcome
A, F, 6	fluticasone aerosol 25µg BID asthma	fluticasone nose spray	insomnia, agitation	days, recovered after dose reduction
B, M, 2	fluticasone aerosol 125µg QID	oxomemazine/-natriumbenzoate/guaifenesine syrup, amoxicillin	agitation	5 months, recovered after withdrawal of fluticasone
C, F, 4	fluticasone aerosol 50µg BID allergic rhinitis	clarithromycine	aggressiveness	dose not changed, outcome unknown
D, F, 7	fluticasone rotadisk 100µg BID	fluticasone nose spray	aggressive reaction	8 days, recovered after withdrawal of fluticasone
E, M, 1	salbutamol areosol 100µg as necessary, fluticasone aerosol 250µg BID asthma	none	aggressiveness	hours, dose not changed, patient has not recovered
F, M, 2	fluticason aerosol 250µg BID bronchial hyperreactivity	none	anxiety, insomnia	1 day, recovered after withdrawal of fluticasone, positive rechallenge
G, M, 0	fluticasone aerosol 50µg BID asthma	salbutamol	abnormal crying, hyperactivity	1 day, recovered after withdrawal of fluticason

Patient, Sex, age	Drug Indication for use	Concomitant medication	ADR	Time to onset, outcome
H, M, 8	fluticasone aerosol 250µg BID	salbutamol, terbutaline	agitation, abnormal behaviour	recoverd after withdrawal of fluticason
I, F, 4	fluticasone 50µg BID, pulmonary irritation	none	aggressiveness	recovered after withdrawal of fluticason
J, F, 4	fluticasone aerosol 125µg BID bronchial hyperreactvity	salbutamol	hyperactive behaviour	hours, dose not changed, outcome unknown
K, F, 3	fluticasone 125µg BID, asthma	salbutamol	aggressive reaction, agitation	4 days, dose reduced, outcome unknown
L, M, 5	fluticason aerosol 25µg BID, salbutamol 200µg QID	none	aggressive reaction, behaviour abnormal	Not reported, recovered after withdrawal of fluticason
M, M, 6	fluticasone aerosol 50µg BID asthma	salbutamol	Autism infantile, hyperactive behavior, aggressive reaction	9 days, recovered after withdrawal of fluticasone

Table 2. reports of behavioural changes associated with the use of the combination fluticasone/salmeterol

Patient, Sex, age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, outcome
N, M, 8	fluticasone/salmeterol 250/50 µg BID	fluticason nose spray, salbutamol. desloratadine, montelukast and Oralgen pollen	behaviour abnormal	symptoms appeared after withdrawal of the drug, outcome unknown
O, M, 8	fluticasone/salmeterol 100/50 µg asthma	none	anxiety	6 weeks, recovered after withdrawal of the drug
P, F, 6	fluticasone/salmeterol 50/25µg BID asthma	none	confusion, cognitive deterioration	weeks recovered after withdrawal of the drug
Q, F, 0	fluticason/salmeterol 125/25µg bronchial irritation	salbutamol	hyperactive behaviour	latency not reported, recoverd after withdrawal of the drug

Other sources of information

Literature

Oral administration of corticosteroids has been associated with psychiatric adverse drug reactions. Corticosteroid-induced adverse psychiatric effects have been reviewed by Patten and Neutel [3].

Behavioural changes in children have also been observed in association with the inhalation corticosteroid budesonide.

In a prospective intervention study the asscociation of budesonide and neuropsychological changes in 60 pre-school children with recently diagnosed asthma was investigated. The children used low doses of budesonide (100-200µg) but when they had symptoms of upper respiratory tract infection the dose was increased to 200µg QID for 3 days followed by 200µg BID for 4 days. At 18 months follow up, 15% of the parents reported that their children had experienced neuropsychological adverse drug reactions. The adverse reactions disappeared when the medication was terminated and re-occurred when the inhalation of corticosteroids was reinitiated at higher doses. Aggressiveness was the most common adverse reaction but hyperactivity, mood changes and excitability were also noticed [4].

Connett and Lenny presented a case series where four cases of acute behavioural disturbances were reported in children aged 2 to 3 years treated with oral inhalation of budesonide in doses 400 µg 2 to 3 times daily. Onset of symptoms occurred within 48 hours after initiation of budesonide or during increase to this dose from a lower dose, and included bedwetting, aggressiveness, insomnia, night screaming, temper tantrums, and hyperactivity. These symptoms resolved after dose reduction or substitution with inhaled beclomethasone, and returned upon rechallenge in 2 children [5].

Databases

The Lareb database contains 50 reports of ADRs in association with children's (0-18 years) use of fluticason inhalation. 26% of these reports concern behavioural changes. Similarly there are 9 ADR reports received with the use of the combination salmeterol/fluticason. In 4 (44%) reports, behavioural changes are reported.

Mechanism

The mechanisme of corticosteroid-induced psychiatric and behavioural changes are not known.

Prescription data

Total number of prescriptions of SSRIs and venlafaxine in the Netherlands is shown in table 3.

Table 3. total number of prescriptions of fluticason and fluticason/salmeterol per year, 2000-2005 (Source: GIP College voor Zorgverzekeringen, Diemen)

	2001	2002	2003	2004	2005
fluticason (Flixotide ®)	881,630	861 740	822,760	821,100	765 370
fluticason/salmeterol (Seretide ®)	421,410	593,410	786,070	951,880	1,084,600

Discussion

Behavioural changes in children in association with the use of inhalated fluticason have not been described in the literature. However, psychiatric effects have been described with the use of oral corticosteroids as well as with budesonide inhalation.

The SPC of the combination fluticasone/salmeterol (Seretide®)mentions behavioural changes such as hyperactivity and agitation as possible ADRs of the drug. GlaxoSmithKline (GSK), the manufacturer of Seretide® says that the behavioural changes probably are due to the salmeterol component. Hyperactivity and hallucinations are listed as possible ADRs with the use of short acting β_2-sympathicomimeticum salbutamol (Ventolin®) [2,6]. According to GSK they have not received any reports of behavioural changes after fluticasone use only.

Although hyperactivity and behavioural changes are listed for β_2 the evidence herefore is weak. *Hadjikoumi et al* investigated the effect of salbutamol on hyperactivity in children. Nineteen asthmatic children (2-6 years) were assessed in a standardised setting before and after administration of nebulised salbutamol and placebo. Neither parental report nor observer rating suggested any significant increase in the child's activity [7].

In our reports 6 patients who used fluticasone only, also received treatment with salbutamol. In the cases where fluticasone was withdrawn, the behavioural changes disappeared. In one of the reports, salbutamol was also reported as suspect drug, in all the other cases the reporter did not see a causal relationship between the ADR and salbutamol. These results supports our theory that fluticasone is responsible for the behavioural changes in the children.

Conclusion

The Netherlands Pharmacovigilance Centre Lareb has received 17 reports of behavioural changes in children associated with the use of fluticasone or fluticasone/salmeterol.

Behavioural changes associated with the use of fluticasone are described in a recent article by de Vries et al [8]. In addition, there have been reports of psychiatric effects with the use of oral corticosteroids and with budesonide inhalation which makes it possbile that it is a group effect.

References

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