

Neuropsychologic changes and inhaled corticosteroids

To the Editor:

It is a well-known fact that high doses of oral steroids can cause neuropsychologic and behavioral changes and even psychosis.¹ There are sporadic case reports on similar reactions in adults and children treated with inhaled corticosteroids.²⁻⁴ In 1998, the Pharmacovigilance Unit at the Swedish Medical Product Agency presented a preliminary report of 37 cases of neuropsychologic disturbances in association with inhalation of budesonide over 10 years.⁵ Twenty-eight of these reports concerned children.

The same year we started a prospective intervention study with 60 preschool children with recently diagnosed asthma. The study was approved by the regional Research Ethics Committee. At the follow-up after 3 and 6 months, several parents told us about possible neuropsychologic changes that they thought were due to inhalation of corticosteroids. We decided to investigate this potential connection at the follow-up visit after 18 months.

The children in this study were told that they should start a treatment with 200 µg of budesonide administered 4 times a day for 3 days through a spacer, followed by 200 µg ×2 for 4 days when they had symptoms of an upper respiratory tract infection (URTI). Most of them were receiving regular treatment with 100 to 200 µg of budesonide. At the 18-month follow-up, the doctor asked a specific question (in addition to others from a questionnaire): "Have you noticed any negative effect on your child from the asthma medication? If yes, in what way?"

The parents of 9 (15%) children reported that their children had experienced suspect neuropsychologic adverse effects (Table I). These adverse effects had disappeared when the medication was terminated and recurred when the inhalation of corticosteroids was reinitiated at higher doses. The Pharmacovigilance Unit considered that it was a connection between these adverse effects and the medication. The reactions were classified as not serious.

As can be seen, aggressiveness was the most common adverse effect, but hyperactivity, mood changes, and excitability were also noticed. Enuresis was reported in one case and recurred when treatment was given again.

The adverse effects were seen within 2 days from when the children started the relatively high dose of budesonide because of a URTI. The majority of the children could return to the maintenance dose afterward without any problem.

Two children (nos. 5 and 9) were reported to have a tendency for unrest and hyperactivity even before they started treatment with budesonide, but according to their parents, this was noticeably more prominent when they inhaled high doses.

A summary of the cases reported to The Pharmacovigilance Unit at the Medical Product

Agency in Sweden in the summer of 2003 since the start of treatment with inhaled steroids shows that there are 619 reports of adverse effects, and in 549 cases the Pharmacovigilance Unit considered a connection between the medication and the adverse event as plausible. Neuropsychologic adverse effects were reported in 273 cases, and in 260 the connection was considered plausible. The majority of neuropsychologic adverse effects affected children and teenagers.

Sleep disturbances, hallucinations, and depression were symptoms reported in addition to those mentioned above. Medications used were budesonide in 230 cases, fluticasone propionate in 31 cases, and beclomethasone dipropionate in 12 cases. These figures mirror the current patterns of inhaled corticosteroid prescription and use in Sweden. Thus these side effects seem to be a class effect and not an adverse effect unique to budesonide.

There could be alternative explanations for our clinical adverse reports. Newspapers had written about the possible adverse effects during 1998, but several of the parents who reported these adverse effects had never heard of the connection between these symptoms and inhalation of corticosteroids. Viral infections can cause behavioral disturbances by themselves, and another explanation could be that the asthma in itself could lead to these kinds of neuropsychologic symptoms. However, the only connection that has been proved is with severe nighttime asthma symptoms and behavioral disturbances,⁶ and none of our children reported this.

A few of our children had also inhaled some doses of β₂-agonists, but most of them started the a high dose of budesonide in connection with a URTI to prevent a worsening of their asthma and never had any asthma symptoms. Although the pharmacopoeia lists hyperactivity and behavioral disturbances as effects of β₂-agonists, the evidence for this is weak,⁷ and a review concluded that β₂-agonists have no severe effects on children's behavior.⁸

A randomized, double-blind study comparing beclomethasone with theophylline in children 6 to 17 years of age found no evidence for behavioral changes with inhaled corticosteroids.⁹ In a 5-year, randomized, double-blind study including extensive psychologic evaluation, 200 µg of budesonide ×2 in children 5 to 12 years of age was actually found to cause less depressive feelings compared with placebo.¹⁰

On the other hand, it has been proved that inhaled steroids can have systemic effects, such as adrenocortical

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TABLE I. Dose of budesonide and type of adverse effects

	Age (y)	Maintenance dose of budesonide	Dose of budesonide when adverse effects were reported	Adverse effect reported
1	2:4	100 µg × 1	200 µg × 4	Irritability, depression
2	5:0	200 µg × 1	200 µg × 4	Aggressiveness
3	4:0	100 µg × 2	>200 µg	Anger
4	3:0	—	200 µg × 4	Aggressiveness, excitability
5	2:3	200 µg × 1	200 µg × 2	Mood changes
6	5:0	200 µg × 1	200 µg × 4	Aggressiveness, excitability
7	4:10	200 µg × 2	200 µg × 4	Enuresis, hyperactivity
8	1:6	200 µg × 1	200 µg × 2	Hyperactivity, unrest
9	1:10	200 µg × 1	200 µg × 4	Hyperactivity, attention deficit

insufficiency.¹¹ Neuropsychologic changes are probably uncommon, but clinical experience tell us that it might not be rare in preschoolers. The relatively high number of adverse reports to the Pharmacovigilance Unit at the Medical Product Agency and our findings that 15% of the children in a prospective asthma study reported these kinds of adverse symptoms strengthens this notion. It is also obvious that if this phenomenon does exist, it is dose related. The children in this study could be treated effectively with a low dose of inhaled corticosteroids, often in combination with chromolyns, antileukotrienes, and/or β_2 -agonists without side effects.

A double-blind provocation study would be necessary to prove the possible connection between inhaled corticosteroids and neuropsychologic disturbances in preschool children, but this has up to now not been performed.

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Interpretation of isolated positive skin test results for mesquite tree pollen

To the Editor:

Skin testing is an essential part of the evaluation of patients with suspected IgE-mediated diseases such as allergic rhinitis. Positive skin tests are supposed to represent the presence of specific IgE antibodies to the allergens tested. IgE antibodies to specific allergens can also be detected by *in vitro* assays such as ImmunoCAP (Pharmacia Diagnostics, Uppsala, Sweden). There is a general tendency to make IgE antibodies (and have multiple positive skin tests) or not. Thus, it is unusual to see skin testing results positive for only a single allergen. We noted that we often see patients whose only positive skin test result is to mesquite pollen. This is particularly striking because mesquite trees are very rare in our location. We test for this pollen nonetheless because our military population moves frequently around the country and the world. In contrast, olive tree is thought to be our most allergenic tree pollen and is very common in our location, yet we seldom see olive tree as the sole positive skin test result. There are at least 2 possible explanations for these isolated positive skin test results to mesquite: either mesquite pollen is particularly allergenic, or the allergenic extract of mesquite pollen used for skin testing is capable of causing a non-IgE-mediated skin reaction, either direct mast cell degranulation or an irritant response. Knowing the likelihood of each of these possibilities would allow clinicians looking at an isolated positive skin test result to mesquite to determine the likelihood that it represented a true-positive result.

Consecutive full aeroallergen skin test panels (consisting of 6 grasses, 15 trees, 11 weeds, 8 molds, cat, dog, cockroach, and 2 dust mites) in our clinic were reviewed to determine how often mesquite was the only positive skin test result of any kind, how often mesquite was the only positive pollen skin test result but with some other nonpollen aeroallergen positive, and how often mesquite