

Perennial rhinitis in the under 4s: A difficult problem to treat safely and effectively?

A comparison of intranasal fluticasone propionate and ketotifen in the treatment of 2–4-year-old children with perennial rhinitis

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To compare the safety and efficacy of fluticasone propionate aqueous nasal spray (FPANS) and oral ketotifen in children aged 2–4 years with perennial rhinitis. A randomized, multicentre, double-blind, double dummy, placebo-controlled study. Paediatric patients between the ages of 2–4 years with perennial rhinitis. Rhinitis symptoms score (parent-rated), clinical evaluation of symptoms (investigator-rated) and adverse event profiles during the treatment period. Patients treated with FPANS had a significant reduction in both the total night-time rhinitis symptom assessment for weeks 4–6 (p-value 0.036), and the total daytime rhinitis symptom score over the same period (p-value 0.049). Generally, except for nasal itching/rubbing over weeks 1–3, the patients taking FPANS had lower recorded symptom scores for all individual symptoms measured. Nasal blockage, in particular, was significantly reduced over the 4–6 week period (p-value 0.027). The overall investigator-rated clinical evaluation showed substantial improvement or improvement in nine of 12 of the children taking FPANS compared with four of 14 taking ketotifen. Finally, there were no reports of serious adverse events, the incidence of drug-related adverse events was low and there was no statistical difference between the groups. FPANS may be an appropriate treatment to control the symptoms of rhinitis in children between 2 and 4 years old.

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Rhinitis is a common disorder in children. Most perennial rhinitis in children is allergic (1). Data on children under the age of 4 years, however are scarce. The diagnosis of allergic rhinitis, especially of perennial allergic rhinitis in very young children can be obscure: not only because the differential diagnosis including adenoid hypertrophy and recurrent upper respiratory tract infections can be difficult to unravel, but also because it is not easy to definitively diagnosis allergic sensitization and its relationship to symptoms (2, 3).

However, in very young children allergic rhinitis is not uncommon (4). In 81 consecutive adenotomies in children with a mean age of 2.2 years, 20% had allergic rhinitis (5). Ninety percent of children with asthma also had rhinitis, and allergic rhinitis increases the chances of developing otitis media and sinusitis (6).

Thus, there is a need for effective once daily therapy for rhinitis in children under the age of 4 years.

At present sodium cromoglycate (7), antihistamines (8) and nasal corticosteroids (9) are

prescribed in young children. Ketotifen (zaditen) is an oral antihistamine with some additional cromoglycate-like activity (10). It is available in syrup form for the treatment of allergic rhinitis, asthma and eczema in children from 2 years of age. In common with other antihistamines it decreases nasal itch, rhinorrhoea and sneezing, but makes little difference to nasal obstruction (7). The treatment of nasal obstruction is important not only because of the burden to the child but also to prevent the child from habitual mouth breathing (11, 12) which is associated with otitis media with effusion (6) and decreased outgrowth of the maxilla (13, 14).

The use of intranasal corticosteroids in young children is controversial, both because of the possibilities of adverse systemic effects and because of problems of the use of nasal sprays. Studies showing effects of intranasal corticosteroids on short-term childhood growth employed high doses of budesonide (15) or beclomethasone (16) (in the latter study on a twice daily basis for a year). Similar effects were not seen with a reduced dose of budesonide given once daily (17), or long-term growth in the treatment of perennial rhinitis (18). Fluticasone propionate aqueous nasal spray (FPANS) is a third generation corticosteroid, which shows minimal intestinal absorption and extensive first pass hepatic metabolism. Intranasal doses of up to 4 mcg for 7 days in man are associated with little or no systemic activity (19). Studies on bone mineral density with FPANS in young children demonstrated no adverse effects (20). It is used in seasonal (21) and perennial rhinitis (22, 23), has been assessed in children over 4 years old and has been found to be more effective than placebo when used at 100 mcg once daily, with an adverse event profile similar to placebo. We wondered whether a local corticosteroid spray was more effective than an antihistamine in reducing symptomatology in very young children. To evaluate this a study was performed on a double-blind, double dummy, placebo-controlled randomized basis to compare FPANS with ketotifen in the treatment of perennial rhinitis, paying particular attention to the safety profiles of both products in the paediatric population aged 2–4 years.

Methods

Patients

Twenty-six children aged between 2 and 4 years (16 male, 10 female), whose parents/guardians consented, were recruited from the paediatric/ENT clinic of two centres. Diagnosis of perennial

rhinitis was defined as two or more of the following symptoms present for more than 2 weeks at a time, recurring over a 6-month period: nasal blockage, rhinorrhoea, sneezing, nasal itching or rubbing. In all patients skin prick testing or radio allergosorbent test (RAST) examination was performed for aeroallergens and food allergens. Moreover, general history, ENT history and medication were noted. Moreover, a total standardized ENT examination was performed. Patients were excluded on the basis of requirements for inhaled or intranasal corticosteroids, sodium cromoglycate or antihistamines, use of systemic corticosteroids, presence of nasal polyps or other anatomical deformations, presence of other severe illness, e.g. cleft palate, concurrent nasal infections or contraindications to steroids. Forty patients were recruited to a run-in period of 2 weeks where they continued with their normal medications (other than the non-permitted medications).

Run-in period

During the run-in period parents of the children completed a diary card in which they rated the symptoms of their child twice daily. In the morning, the symptoms nasal blockage on waking, sneezing, runny nose, nasal itching/rubbing, snoring (previous night) were scored on a 0–3 (no symptoms–severe) scale and the number of night-time awakenings on a 0–3 scale (0, no times awake; 1, one time awake; 3, three times or more awake). In the evening, the symptoms nasal blockage during the day, sneezing, runny nose, and nasal itching/rubbing were scored on a 0–3 scale. Patients were included into the study when the total symptoms score was > 7 per day in the last 3 days of the run-in period.

Study period

Following completion of the run-in period, 26 patients who fulfilled the inclusion criteria were randomly allocated to treatment groups where they received either FPANS 100 mcg once daily plus oral placebo, or oral ketotifen 1 mg once daily plus intranasal placebo, for 6 weeks. During this period the parents/legal guardians of the patients were asked to complete a daily record card in the morning and the evening, describing the child's rhinitis scores on a daily basis. At clinic visits, a number of nasal assessments, symptom scoring and patient compliance were checked along with monitoring of adverse events, oral candidiasis and requirements for 'new' medications. At the end of the treatment

period the investigator was asked to assess whether or not in their opinion the symptoms that the patient had been displaying throughout had improved, stayed the same or got worse. The study was approved by the medical ethical committee in both hospitals and informed consent forms were signed by all parents.

Statistical analysis

Data analysis was performed on an efficacy evaluable population, which was based on the intent-to-treat population but excluded patients who had serious protocol violations. The data were analysed using SAS (release 6.12). The mean total daytime and night-time scores were summarized over baseline, weeks 1–3 and 4–6. An assessment of differences in scores between the treatment groups was analysed using ANCOVA, using the mean baseline score as the covariate. If normality assumptions were not met then the Wilcoxon rank sum test was used. Results are expressed as adjusted mean scores $\pm$ s.e. The investigator's overall rhinitis symptoms assessment at visit 4 was analysed using the Cochran-Mantel-Haenszel test and results are expressed in actual numbers and percentages of patients who illustrated one of the categories listed. Adverse events were summarized and listed accordingly.

Results

Rhinitis symptom and nasal assessment

At randomization of the 26 patients who were randomized, 12 had positive skin prick test/RAST for at least one allergen (five in the FPANS group and seven in the ketotifen group). Interestingly all but one child (milk) were sensitized against aeroallergens (five grass pollen, seven house dust mite (HDM), two cat, three feathers, three *Cladosporium*). All but two children complained of nasal blockage, all but one had rhinorrhoea and 85% had nasal itching/nose rubbing. Only 12% had sneezing or postnasal drip.

On examination, 81% of the children showed turbinate swelling in both nostrils and abnormal colour of the mucosa. The colour was livid in half of the children and red in the other half. All but one child showed nasal secretions. There were no significant differences between the two groups. Of the 26 patients, 23 patients (11 in the FPANS group and 12 in the ketotifen group) could be evaluated.

At the final visit after 6 weeks, 70% of the FPANS group had a patent nasal airway com-

pared with 22% in the ketotifen group ($p = 0.046$). All but one child in the FPANS group (91%) did not have nasal itching/nose rubbing, compared with 70% in the ketotifen group ($p = 0.054$). None of the patients in the FPANS group had sneezing or postnasal drip, and only two in the ketotifen group had postnasal drip.

None of the patients in FPANS group had turbinate swelling compared with four in the ketotifen group (one patient, only one nostril). The colour of the mucosa was normal in 70% in the FPANS group compared with 22% in the ketotifen group. Secretions were found in two of three and crusts in half of the children in both groups.

Generally, except for nasal itching/rubbing over weeks 1–3, the patients taking FPANS had lower recorded symptom scores for all individual symptoms measured, although they did not reach significance except for nasal blockage, which was significantly reduced over the 4–6-week period (p -value 0.027). The overall investigator-rated clinical evaluation showed substantial improvement or improvement in nine of 12 of the children taking FPANS compared with four of 14 taking ketotifen (Fig. 1).

Daytime and night-time scores

Patients treated with FPANS had a significant reduction in the total night-time rhinitis symptom assessment for weeks 4–6 (p -value 0.036), and a significantly reduced total daytime rhinitis symptom score over the same period (p -value 0.049). The corresponding measurements over weeks 1–3 for both total daytime and total night-times symptom scores were reduced in the fluticasone group but this difference was not statistically significant (Tables 1 and 2).

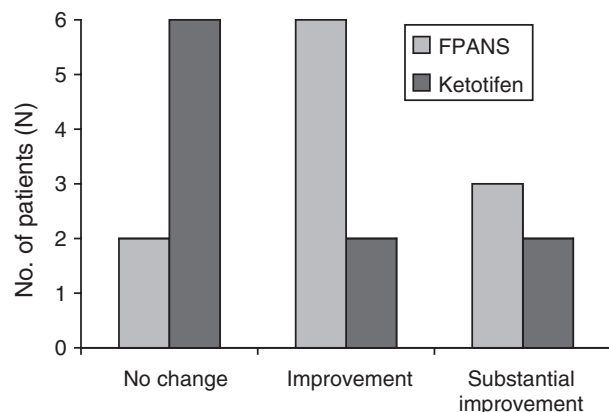


Fig. 1. Investigators assessment of overall rhinitis symptoms at visit 4: intent to treat population.

Table 1. Analysis of patients night-time rhinitis symptoms assessment: efficacy evaluable population (n = 23)

Symptom	Weeks 1–3			Weeks 4–6		
	FPANS	Ketotifen	p-value	FPANS	Ketotifen	p-value
Total night-time symptoms score						
Adjusted total mean	4.7	6.2	0.055 (NS)	4.2	6.5	0.036
Standard error	0.5	0.5		0.7	0.7	*
Nasal blockage						
Adjusted mean	1.3	1.7	0.240 (NS)	1.1	2.0	0.027
Standard error	0.2	0.2		0.3	0.3	*
Sneezing						
Median	0.3	0.8	0.211 (NS)	0.1	0.7	0.262 (NS)
Nasal itching/nose rubbing						
Median	0.6	0.9	0.393 (NS)	0.3	0.7	0.811 (NS)
Rhinorrhoea						
Adjusted mean	1.1	1.6	0.092 (NS)	1.1	1.6	0.120 (NS)
Standard error	0.2	0.2		0.2	0.2	
Snoring						
Adjusted mean	1.2	1.2	0.891 (NS)	1.0	1.2	0.531 (NS)
Standard error	0.1	0.1		0.2	0.2	
Percentage of undisturbed nights						
Median	41.0	33.8	0.311 (NS)	35.7	50.0	1.00 (NS)

Significance: *p < 0.05; NS, not significant; FPANS, fluticasone propionate aqueous nasal spray.

Table 2. Analysis of patients daytime rhinitis symptoms assessment: efficacy evaluable population (n = 23)

Symptom	Weeks 1–3			Weeks 4–6		
	FPANS	Ketotifen	p-value	FPANS	Ketotifen	p-value
Total day-time symptoms score						
Adjusted total mean	4.3	5.1	0.274 (NS)	3.6	5.5	0.049
Standard error	0.5	0.5		0.6	0.6	*
Nasal blockage						
Adjusted mean	1.4	1.7	0.277 (NS)	1.1	1.8	0.101 (NS)
Standard error	0.2	0.2		0.3	0.3	
Sneezing						
Median	0.3	0.9	0.434 (NS)	0.4	0.8	0.541 (NS)
Nasal itching/nose rubbing						
Adjusted mean	0.9	0.8	0.536 (NS)	0.7	1.0	0.360 (NS)
Standard error	0.1	0.1		0.2	0.2	
Rhinorrhoea						
Adjusted mean	1.3	1.7	0.35 (NS)	1.1	1.8	0.149 (NS)
Standard error	0.3	0.3		0.3	0.3	

Significance: *p < 0.05; NS, not significant; FPANS, fluticasone propionate aqueous nasal spray.

Finally, there were no reports of serious adverse events at all. The incidence of adverse events that were assessed as being related to the drug treatment, was very low and with no statistical difference between the groups.

Discussion

This study shows that FPANS is an effective treatment for children aged 2–4 years with perennial rhinitis and that it is more effective than oral ketotifen. The diagnosis of allergic rhinitis, especially of perennial allergic rhinitis in very young children can be obscure: not only because the differential diagnosis including adenoid hypertrophy and recurrent upper respiratory tract infections can be difficult to unravel, but also because it is not easy to definitively diagnosis allergic sensitization and its relationship to symptoms (2, 3). In this study, we have chosen to include children with and without proven sensitization to allergens because in clinical practice it is often not possible to differentiate between allergic and non-allergic rhinitis. Moreover, there is quite some evidence that many young children with rhinitis show sensitization to aeroallergens sometimes years after.

In principle the treatment of (allergic) rhinitis in children does not differ from that in adults (7). In a meta-analysis of randomized-controlled trials comparing intranasal corticosteroids with oral antihistamines Weiner showed that intranasal corticosteroids are more effective than antihistamines (24). The goal of the clinician in selecting the most appropriate treatment regimen for paediatric allergic rhinitis is to balance the potential risks of treatment with the benefits to the patients. The scarcely available data of the prevalence of rhinitis in (young) children point to a prevalence of 10–20% (5, 25), although figures between 1.3% and 52% have been recorded (26). Main issues in the treatment of allergic rhinitis in young children are: the positive effects on nasal symptoms and thus on quality of life of the child, the potential positive effects on co-morbidities like asthma but also otitis and sinusitis, positive effect on growth of the facial skeleton in the future compared with the potential risks of the treatment, mainly the potential systemic effects of corticosteroid treatment on adrenal gland function, bone metabolism and growth.

If we first look at the potential risks of treatment our first concern is the effect of the treatment on long-term growth. Concerns on growth are mainly based on the high systemic effects of early local corticosteroid treatment molecules-like betamethasone and dexamethasone. The common belief is that low dose local treatment with the newer generation intranasal corticosteroids hardly ever causes systemic effects (27–30). Nonetheless, children with allergic rhinitis often have co-morbidities like asthma and/or eczema and may receive local corticosteroids at different sites. Baraniuk

suggested from a literature review that nasal and bronchial administrations appeared to give equivalent responses and that they can be added up to calculate to total systemic load. He suggests a linear relationship between changes in childhood growth velocity and total topical glucocorticoid dose (31). However, other studies did not show an increase in risk to endogenous adrenal function from adding a nasal corticosteroid when inhaled corticosteroids are used (32). On the contrary, in children with asthma the treatment of the rhinitis and especially the nasal obstruction might reduce asthma symptomatology (33–35) and possibly also the need for inhaled corticosteroids (36). Recent studies suggest that early treatment of the first manifestation of atopy could even prevent the onset of other clinical manifestations (37–39). In conclusion, the potential risks of treatment and the benefits to the patient have to be carefully balanced by the prescribing doctor.

When looking at further beneficial aspects of treating rhinitis in young children treatment of rhinitis, and especially nasal obstruction, in young children is essential to prevent open mouth breathing and the occurrence of an 'adenoid face' which predisposes to high-arched palate, overbite and malocclusion (13, 14, 40, 41). Apart from reduction of symptoms in the upper and lower airways, treatment of rhinitis in (young) children improves the quality of life (42–44). Nasal congestion at night causes sleep disturbance and daytime fatigue. Decreasing nasal congestion with nasal steroids improves sleep, daytime fatigue, and the quality of life of patients with allergic rhinitis (45). This study for the first time shows that local corticosteroid treatment is able to reduce nasal symptomatology and especially nasal obstruction in children aged 2–4 years of age.

Co-morbidities of allergic rhinitis-like chronic middle ear effusions, sinusitis, lymphoid hypertrophy with obstructive sleep apnoea, disordered sleep, and consequent behavioural and educational effects have been reported in children (46–48). Although feasible, data supporting the reduction of these co-morbidities by treatment of the rhinitis are scarce and inconclusive (47, 49). Further studies in young children are needed to further elucidate this point.

Although we have shown that FPANS is an effective treatment in this age group the precise indication for its use should be formulated. Further studies have to be carried out to prove that also in young children local corticosteroids are totally safe. Moreover, efficacy and safety have to be compared with antihistamines and cromoglycate. The long-term effects of nasal obstruction caused by (allergic) rhinitis in asth-

matic and non-asthmatic children have to be further evaluated. The negative effects of long-term open mouth breathing and allergic inflammation in the upper airways have to be put against the potential negative effects of local corticosteroid treatment. For now arguments seem to be in favour of local corticosteroid treatment in all children with rhinitis and persistent nasal blockage and also in children with asthma.

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