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Local safety of intranasal triamcinolone acetonide: clinical and histological aspects of nasal mucosa in the long term treatment of perennial allergic rhinitis *

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SUMMARY

Intranasal corticosteroids are increasingly used to treat allergic rhinitis and their long-term use is generally safe. However, the long-term safety of each molecule should be assessed. The main aim of this multicenter, prospective, randomized, open-label study was to evaluate the effect of triamcinolone acetonide aqueous intranasal spray on nasal mucosal thickness, macroscopic appearance, and mucociliary function. Patients with perennial allergic rhinitis were treated with triamcinolone acetonide 220 µg/day for six months. Nasal biopsies taken before and after treatment were compared with biopsies from patients who had been randomized to oral cetirizine 10 mg day or intranasal beclomethasone dipropionate 400 µg/day. In the evaluable population (n=70), there were no significant differences between groups in terms of histologically evaluated thickness and endoscopically evaluated macroscopic appearance of the nasal mucosa, or indigocarmine saccharine test mucociliary function. In the intent-to-treat population (n=92), there was no difference between treatment groups in the incidence of overall adverse events. This study indicates that sustained treatment with intranasal triamcinolone acetonide does not lead to atrophy of the nasal mucosa or impairment of mucociliary function.

Key words: triamcinolone acetonide, allergic rhinitis, mucosal thickness, nasal atrophy

INTRODUCTION

Intranasal corticosteroids are now recognized as having a high therapeutic index in the management of allergic rhinitis (International Rhinitis Management Working Group, 1994; Mygind and Dahl, 1996). Application of high concentrations of these steroids in the nasal mucosa is associated with an important reduction in inflammatory cells and mediators and associated decrease in clinical symptoms such as sneezing, watery rhinorrhea, and nasal blockage (Baraniuk, 1998; Mygind and Dahl, 1996). The therapeutic effects of intranasal steroids on the classic nasal symptoms such as blockage are greater than those seen with oral antihistamines (Meltzer, 1998; Mygind and Dahl, 1996). When administred at recommended dosages, intranasal corticosteroids are significantly effective without effects on adrenocortical function and the hypothalamic-pituitary axis as commonly reported with oral steroids (Howland et al., 1996; Kopek et al., 1997; Horowitz and Burnet, 1979).

As the benefits of sustained treatment with intranasal corticosteroids have become clear, questions related to the potential long-term effects on the nasal mucosa have naturally emerged. These questions are suggested mainly on the widely recognized atrophic dermatological effects of dermal corticosteroid therapy (Somerina et al., 1984; Stefanovic, 1972). The few studies to date involving histological analysis of nasal tissues after intranasal steroid therapy have documented no evidence of treatment-related atrophy (Orgel et al., 1991; Cheng et al., 1997; Pipkorn et al., 1988). However, any intranasal preparation indicated for long-term use in perennial allergic rhinitis has to be tested for its direct effects on the nasal mucosa.

Triamcinolone acetonide (TAA) is available as an aqueous thixotropic formulation with benzalkonium chloride as a preservative (Nasacort AQ®, Aventis, Paris, France). Large placebo-controlled studies have shown that a 220 µg daily dose of this TAA formulation significantly reduces symptoms of sea-

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sonal and perennial allergic rhinitis (Jeal and Faulds, 1997; Rosenthal et al., 1998; Kobayashi et al., 1995; Koepke et al., 1997; Nayak et al., 1998). Compared to other intranasal corticosteroids, TAA has also proved at least equivalent in terms of efficacy and overall safety (Small et al., 1997; Jeal and Faulds, 1997).

To date, there have been no studies on long-term application of TAA on the nasal mucosa. The purpose of this study was to gauge the local tolerance of this potent intranasal corticosteroid by using morphometric analysis of nasal epithelium and basement membrane, i.e. nasal mucosa in histological definition (nmh) and macroscopic aspects of nasal mucosa, i.e. in macroscopic definition (NMM), before and after six months of treatment. These results were compared with those seen in a similar patient population before and after six months of treatment with a second-generation oral antihistamine, cetirizine, which is indicated for the treatment of seasonal and perennial allergic rhinitis. Histological measurement is the primary measure of safety. All other comparisons are secondary. As a further reference, the effects of TAA on the nasal mucosa were also compared with those of an intranasal corticosteroid, beclomethasone dipropionate (BDP). Finally, based on concerns related to findings of *in vitro* (but not *in vivo*) detrimental effects of the preservative benzalkonium chloride on cilia function in the nasal mucosa (Braat et al., 1995; McMahon et al., 1997), the study included a special evaluation of mucociliary function.

MATERIAL AND METHODS

Patient population and study design

This was a randomized, prospective, parallel-group open study conducted at eight French study centers for mucociliary function and endoscopic evaluation, and one central histology laboratory for NMH thickness evaluation. The study was conducted in accordance with the Declaration of Helsinki and in compliance with all local regulations. Local ethic committees approved the protocol and all patients gave written informed consent to participate.

Males or females aged 18 to 65 with a history of perennial allergic rhinitis of at least one year's duration were recruited. They were required to have had a recent positive skin prick test for house dust mites.

Patients were excluded if they met any of the following criteria: a positive skin prick test to pollen and a positive assay for specific IgE, with or without clinical exacerbation during the pollen season; obstructive specific deviation of the nasal septum, nasal polyps, or any other severe concomitant disorders; laboratory abnormalities; known hypersensitivity to test drugs. Patients were also excluded from participation if they had taken: antihistamines or sodium cromoglycate in the 7 days prior to the inclusion visit; oral or nasal corticosteroids and/or vasoconstrictors in the month prior to the inclusion visit; or corticosteroids or astemizole in the 3 months prior to the inclusion visit. Smokers, pregnant women, women likely to become pregnant were also excluded.

Patients were randomized to receive one of the following treatments: (1) 220 mg TAA (Nasacort AQ®) as two 55 μg sprays in each nostril once daily; (2) 10 μg cetirizine (Zyrtec®) as one tablet orally per day; or (3) 400 μg BDP (Beconase®) as one 50 μg spray in each nostril four times per day. No placebo group was included.

Reports of adverse events were collected along with information on intercurrent illnesses and accidents. Severity and relation to the studied medicines were analyzed. Rhinitis symptom severity was evaluated by patients (using the Visual Analog Scale = VAS) and investigators (using Global Assessment scores of 0-4). Patient compliance was measured by comparing patient diaries with the weight of used bottles or the number of unused tablets.

Nasal biopsy

After mucociliary function evaluation with indigocarmine saccharine liquid test, a local anesthesia with a spray of xylocaine 5% (Astra France) was performed. Then biopsy was taken under endoscopic guidance (Optic 0° or 30°) with a Microfrance forceps (2 mm) at the 2/3 posterior part of the inferior turbinate by ENT. In cases of significant septal deviation, vascular abnormalities, nasal polyps or homeostasis problem, patients were excluded.

Morphometric measurement method

The primary assessment involved quantitative examination of NMH thickness of nasal biopsies taken before treatment (immediately after verification of inclusion criteria = V1) and after 24 weeks of treatment (V4). Biopsies were processed as previously described (Laliberté et al., 2000), briefly: biopsies were fixed at -20°C in acetone containing the protease inhibitors iodoacetamide and phenylmethylsulfonyl for 24 hours. They were embedded in water soluble resin glycol methacrylate (GMA). Sections of 2 μm thickness were cut from the embedded specimen using an ultramicrotome and analyzed to determine thickness, in mm, of the epithelium and/or basement membrane (basement membrane is composed of basal lamina and reticular lamina as discerned by light microscopy). To ensure comparative validity between pre- and post-treatment biopsies, histologists (blinded to treatment groups) attempted to select cutting incidence and area as similar as possible with longitudinal section of epithelium and basement membrane thickness equal all along the measured length. Morphometric measurements were taken over a minimum length of 50 μm. An analysis was also performed on the thickness of the basement membrane only.

Specimens were excluded if they presented poor fixation, absence of epithelium, insufficient length or wrong orientation of epithelium or basement membrane.

Endoscopic evaluation

In addition to taking the biopsy during the pre- and post-treatment visits, clinicians performed a thorough endoscopic evaluation especially focused on the permeability of the nasal fossae, endonasal crusting, and appearence and colour of the mucosal membrane (i.e. NMM).

Mucociliary function evaluation

Before local anesthesia, each patient also underwent an indigo-carmine saccharine liquid test (ICST) for mucociliary function (Kleinschmidt and Witt, 1995). The difference between the time the saccharine colored solution was administered to the time the patient perceived a sweet taste or the physician saw a bluish colour in the oropharynx was reported.

Statistical analysis

Sample size was based on the number of patients required for a two-tailed test with a type I error of 5% and a type II error of 20%. At least 72 patients were required in the evaluable population, which was defined as having a compliance rate of greater than 70% during the study. Assuming a one-in-five exclusion rate, a total population of 90 patients was calculated as necessary to carry out the study. For the biopsy measurement, statistical tests of equivalence were performed on the NMH of patients in all treatment groups. The primary comparison was between TAA and cetirizine. All biopsies analysis were performed as a mixed analysis of covariance (adjusted for the inclusion visit, V1). All quantitative parameters were analyzed using an analysis of variance and Fisher's Exact Tests. Semi-quantitative parameters were analyzed using non-parametric Wilcoxon Rank Tests. Adverse events were compared for the Intent-to-Treat (ITT) population.

RESULTS

Patient demographics and disposition

Ninety two patients were recruited into the study (ITT population) and randomized to one of the three treatment groups. Twenty two of these 92 patients (24%) were excluded from the biopsy analysis: 10 from the TAA group, 5 from the BDP group, and 7 from the cetirizine group. Most of these exclusions (19) were due to non-evaluable nasal biopsy, because of the size or quality of specimen, with an additional 3 due to compliance below 70%, forbidden treatment (surgery) and withdrawn consent.

There were no differences in demographic variables among the three treatment groups in either the ITT population or the total evaluable population (70) (Table 1). One patient in each group had a history of epistaxis or secretions with blood. Three patients in the cetirizine group and 1 in the BDP group had a history of nasal crusts.

Most patients (80) received at least one concomitant medication over the course of the study. Although 7 patients took a prohibited concomitant medication, none were excluded since all deviations had occurred more than a month before the post-treatment biopsy. Median compliance rates were 89.7% for TAA, 87.6% for BDP, and 98.2% for cetirizine groups.

Comparisons of nasal mucosa (NMH) thickness

For each patient the NMH thickness of the biopsy taken before treatment (V1) was compared with that taken after 24 weeks of treatment (V4). For all three treatment groups the NMH thickness decreased slightly from V1 to V4 (Figure 1). The mean decrease from baseline for all 70 evaluable patients was –7.6 μm +/–4.06, an overall trend that was not statistically significant (p=0.07) (Table 2). Moreover, no statistically significant differences between treatment groups were found with regard to the magnitude of this general decrease in NMH thickness (p=0.95 for treatment effect). When the changes from baseline in basement membrane thickness were considered separately, the mean overall change was 0.0 μm +/–0.52 with no significant differences between treatment groups (p=0.10). This demonstrated that the epithelium is responsible of the reduction of NMH thickness (Table 2).

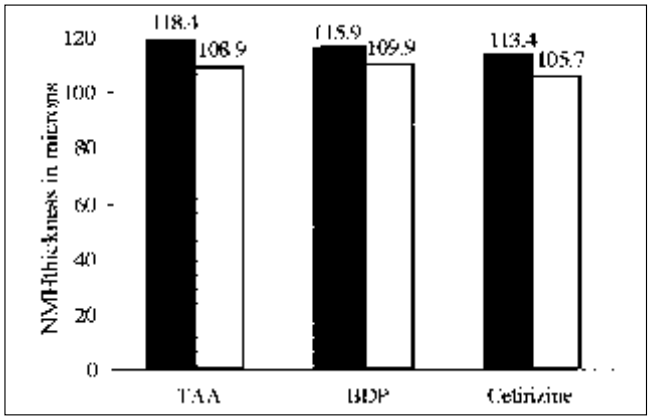
Table 1. Demographics characteristics of the evaluable population.

Characteristic		TAA	BDP	Cetirizine
Number		21	26	23
Sex	Male	11	14	17
	Female	10	12	6
Age (yrs)	mean	27.0	26.4	28.0
	SD	9.15	9.90	8.65
Duration of PAR (yrs)	mean	11.7	8.5	11.2
	SD	5.40	5.81	6.81

Table 2. Changes in nasal mucosa thickness before and after six months of treatment from patients with perennial allergic rhinitis.

	TAA (n=21)	BDP (n=26)	Cetirizine (n=23)	Total (n=70)
Total epithelium + membrane, mean (μm± SE*)	-9.1(6.8)	-6.0(7.6)	-8.2(6.7)	-7.6(4.06)8
p-value for treatment effect		0.95		
Basement membrane only, mean (μm± SE*)	1.7(1.1)	-1.0(0.9)	-0.3(0.7)	0.0(0.52)
p-value for treatment effect		0.10		

*SE = standard error



■ V1, mean at visit 1 (0 weeks)
□ V2, adjusted mean at visit 4 (24 weeks)

Figure 1. Comparison of nasal mucosal thickness (NMH) before (V1) and after (V4) six months of treatment from patients with perennial allergic rhinitis.

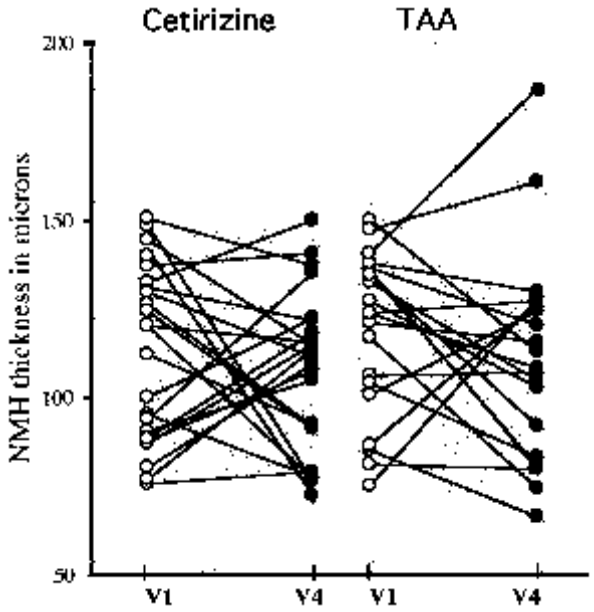


Figure 2. Individual NMH thickness measurement on biopsy sections before (V1) and after 6 months (V4) of treatment from patients with perennial allergic rhinitis. left, with cetirizine, right, with TAA.

Table 3. Mucociliary function before and after six months of treatment for perennial allergic rhinitis: Distribution of changes in indigocarmine saccharine test (ICST) in ITT population (90).

ICST Parameter	Change (minutes)	Treatment Group		
		TAA 29	BDP 31	cetirizine 30
Sweet taste	−30 < t > −20	3	3	0
	−20 < t > − 5	2	7	5
	− 5 < t > + 5	20	14	24
	+ 5 < t > +20	3	3	0
	+20 < t > +30	1	4	1
p=0.58 (Kruskal-Wallis) between treatment groups				
Bluish stain in oropharynx	−30 < t > −20	2	2	2
	−20 < t > − 5	6	6	8
	− 5 < t > + 5	18	17	17
	+ 5 < t > +20	2	4	2
	+20 < t > +30	1	2	1
p=0.33 (Kruskal-Wallis) between treatment groups				

When individual data points where presented paired for TAA and cetirizine (Figure 2), both treatment groups exhibited a decrease from baseline values by visit 4 but these changes were considered not statistically different (p=0.95). However, individually, more patients are concerned by a decrease of NMH thickness in the TAA group.

Other biopsy- and endoscopy-related mucosal findings

The most common epithelium present was respiratory, pseudostratified including numerous mucous cells, ciliated cells and basal cells. Few patients exhibited metaplastic epithelium at baseline or posttreatment and the distribution was similar across all groups. No quantitative or qualitative treatment-related differences in nasal epithelium were noticed in any treatment group. Moreover, we never found epithelium destruction in the biopsies studied here.

Development of endonasal crusts was observed in 9 patients by the end of the treatment period, 4 from the TAA group, 3 from the cetirizine group, and 2 from the BDP group. None of these patients reported the crusting as an adverse event. No major or minor endoscopic findings (oedema and colour of mucosa in inferior and middle turbinate, vascular spot at septum nasal) were reported during the study for all 3 ITT patient groups.

Mucociliary apparatus

Most of the patients in ITT population, in all treatment groups had no increase or decrease in ICST times of more than 5 minutes (Table 3) indicating no effect of these intranasal therapies on mucociliary function in the upper airway epithelium. Analysis of the medians showed no significant difference between treatment groups with regard to these changes in ICST times. The mean times to perception of a sweet taste or appearance of a blue stain at post treatment ICST were 9.3/10.7 minutes in the TAA group, 12.5/12.2 minutes in the BDP group, and 8.3/10.8 minutes in the cetirizine group.

Adverse events

A total of 82 patients in the ITT population (89%) had at least one adverse event during the study period, with no statistical difference between treatment groups in terms of overall frequency (p=0.22). Epistaxis (26 patients), pharyngitis (24 patients), and headaches (33 patients) were the most commonly reported adverse events. Seven adverse events were considered severe, although none were related to the treatment. With regard to the treatment-related adverse events, analysis of each type of adverse event revealed statistical differences between groups. All three cases of treatment-related somnolence were observed in the cetirizine group. BDP, but not TAA, was associated with a significantly higher incidence of epitaxis compared with cetirizine (p=0.022).

Efficacy evaluation

The Clinician's Global Opinion showed a significant improvement in allergic rhinitis symptoms in all treatment groups. Results of the VAS also documented an improvement in symptoms during the treatment period but this improvement did not attain overall statistical significance. There were no significant between-treatment differences in either Global Assessment or VAS.

DISCUSSION

The aim of this study was to evaluate the local tolerance of the nasal mucosa to long-term treatment with TAA, a widely used intranasal corticosteroid. Patients with perennial allergic rhinitis were treated for six months with intranasal TAA. Biopsies of the nasal epithelia were taken before and after treatment and checked histologically for signs of atrophy. Clinicians also performed endoscopic evaluations and mucociliary testing of the nasal mucosa.

Neither the histologic nor the macroscopic appearance of the intranasal mucosa in 21 patients receiving TAA were statistically different from those obtained from a parallel group of 23 patients receiving an oral antihistamine. However, change from baseline analyses revealed an overall 10% decrease in the thickness of the NMH for all patients, regardless of treatment group. Calderon et al. (1994) have shown that the thickness of nasal epithelium was significantly greater in biopsy specimens of patients displaying symptoms of perennial rhinitis than patients with seasonal rhinitis. This may be caused by perennial exposure to the allergen. This could be related to the decrease observed in the NMH (mainly due to epithelium thickness decrease) of the patients treated in this study, which may have decrease due to the treatment relief of their symptoms rather than due to an adverse event related to the treatment. This is also valuable for cetirizine as reported by Ciprandi et al. (1997) who have shown a reduction of inflammatory variable in allergic rhinitis after a continuous administration of cetirizine. As a matter of fact, if there was no statistical difference between the mean decrease thickness of NMH between TAA (-9.1 μm) and cetirizine (-8.2 μm), an individual analysis of change from baseline to the end of treatment showed that more patients were concerned by a decrease of NMH thickness in the TAA group suggesting a better efficiency of TAA on this parameter.

The lack of significant metaplastic epithelium in the TAA treatment group provides further histological evidence of a lack of an adverse cellular (atrophic) effect of the corticosteroid on local nasal tissues. Macroscopically, NMA in all treated groups were also normal. Although the number of nasal crusts was higher at the end of the treatment period, none of these were considered adverse events and they were equally distributed between treatment groups.

The lack of histological and macroscopic changes following intranasal steroid therapy confirms findings from studies with other intranasal corticosteroids (Pipkorn et al., 1988; Orgel et al., 1991; Cheng et al., 1997) and more recently with fluticasone propionate and mometasone furoate (Holm et al., 1998; Minshall et al., 1998). This supports the notion that long term treatment with intranasal corticoids did not cause atrophic changes within the nasal mucosa, in opposition to the well-known dermal thinning effects of topical glucocorticoids, for reasons probably related to differences between dermal and mucosal cell turnover or sensitivity (Pipkorn et al., 1988); and thus atrophy of the mucosa is not a clinical issue in intranasal steroid therapy of perennial rhinitis.

Because normal ciliary function is critical to proper clearance of the nose and paranasal sinuses, and because benzalkonium chloride in intranasal steroids has previously been linked to *in vivo* cessation of ciliary movement (Hoffman et al., 1998; McMahon et al., 1997), *in vivo* tests of products containing this preservative are warranted. Results of the ICST analysis in this study show clearly that long-term treatment with a thixotropic formulation of TAA and benzalkonium chloride has no effect on mucociliary function. This is consistent with previous findings with other intranasal corticosteroids (Braat et al., 1995) and indicates that TAA will not impair the functions of the ciliated epithelium.

No treatment-related severe adverse events were reported in this study, confirming previous findings of TAA nasal spray as a generally well tolerated therapy (Jeal and Faulds, 1997). Although reports of a few specific treatment-related adverse events (e.g., epistaxis) were higher in both corticosteroid treatment groups than the cetirizine group, the overall rates were not significantly different. However, the open-label nature of the study was not adequate to compare the side effect profiles.

In terms of treatment efficacy, both the clinician's assessment and the patient's self-rating VAS indicated that all treatment groups experienced similar levels of relief from their symptoms. However, the study included no placebo control and was unblinded (for the clinical issue); thus, the design was not optimized to reveal differences between treatment groups.

In summary, no endoscopic nor histological evidence of mucosal atrophy was observed following six months of treatment with TAA. This intranasal spray did not retard mucociliary function and it was well tolerated at the dose administered. Thus benign local safety profile indicates that TAA remains an appropriate choice for long-term treatment of allergic rhinitis.

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