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A Risk-Benefit Assessment of Intranasal Triamcinolone Acetonide in Allergic Rhinitis

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Abstract

The efficacy of intranasal triamcinolone acetonide in seasonal and allergic rhinitis has been evaluated in clinical trials and has been compared with antihistamines and other intranasal corticosteroids. Intranasal corticosteroids are either as equally effective as or more effective than comparative drugs. Intranasal corticosteroids are particularly useful as they decrease membrane permeability and inhibit both early and late phase reactions to allergens. They minimise the nasal secretory response and reduce the sensitivity of local nasal irritant receptors. A potential benefit of topical application is the flushing action of the nasal mucosa, which may reduce allergens and secretions.

In addition to seasonal and perennial rhinitis, intranasal corticosteroids have additional benefits when used to reduce inflammation in the treatment of sinusitis and may help in decreasing secondary rhinovirus infections. Furthermore, suboptimal control of asthma can be avoided by treatment of allergic rhinitis with intranasal corticosteroids.

In clinical trials, common adverse effects for triamcinolone acetonide include sneezing, dry mucosa, nasal irritation, sinus discomfort, throat discomfort, epistaxis and headache. Nasal candidiasis and septal perforation have been reported, although rarely. Posterior subcapsular cataract formation has not been seen with triamcinolone acetonide.

Recent literature evaluating systemic absorption of intranasal corticosteroids have shown surprising results where significant absorption has occurred with intranasal budesonide and fluticasone propionate. Growth and hypothalamic pituitary axis (HPA) function studies have been reviewed, with some intranasal corticosteroids showing changes with continual use. A retrospective study in children receiving daily triamcinolone acetonide for 12 months showed no effect on height and bodyweight. Triamcinolone acetonide at standard dosages (110 or 220μg once or twice a day) does not appear to suppress adrenal gland function and is effective in relieving most symptoms of allergic rhinitis.

The International Consensus Conference Proceedings on Rhinitis now currently recommends the use of intranasal corticosteroids as first line therapy, since they have been found to be well tolerated and effective with minimal adverse effects and, specifically, no cognitive impairment.

The recommended maximum dose of aqueous triamcinolone acetonide in adults and children is 220μg once a day. The aerosol form may be recommended in children between 7 and 12 years old, up to 440μg once a day or in divided doses. Duration of allergy treatment is generally for the length of each allergy season. If symptoms are perennial, then a reduction of dosage is made to the lowest effective dose with monitoring every 3 months for risk and benefit assessment. Complications to watch for include bleeding, and possible septal perforation and nasal candidiasis, although these are rare.

Allergic rhinitis affects more than 35 to 40 million children and adults in the US.[1] Although it does not threaten lives, it has a significant impact from both a quality of life and cost perspective.

Allergic rhinitis is an immunologically-mediated disease and is caused by an antigen-antibody reaction involving immunoglobulin E (IgE). IgE antibodies are bound to the surface of mast cells located in the mucous membranes of nasal tissues and conjunctiva. The mast cells are therefore positioned to come into direct contact with airborne allergens. In predisposed individuals, sensitised mast cells primed by allergens such as pollens, moulds, dust, mites and animal dander release a number of chemical mediators including histamines, leukotrienes, kinins and prostaglandins. These mediators trigger the tissue changes that cause the classic symptoms of allergic rhinitis.

The symptoms of allergic rhinitis can be seasonal or perennial. With seasonal allergic rhinitis, symptoms occur in the spring or fall in response to specific pollens and, in some cases, moulds. The symptoms of perennial allergic rhinitis occur throughout the year and are due to housedust mite, mould, feathers and animal dander, with seasonal flare-ups in some individuals secondary to pollen allergies.

The treatment of allergic rhinitis involves a 3-fold approach of avoidance of specific allergens, pharmacotherapy to prevent or alleviate symptoms, and immunotherapy.[2] Successful treatment of allergic rhinitis requires that the correct diagnosis is made and that appropriate therapy is delivered to the target organ. Intranasal corticosteroids such as triamcinolone acetonide are most effective in this situation.[1-6] These agents have a 2-fold advantage of delivering the active corticosteroid drug to the nasal mucosa with minimal systemic adverse effects.[7,8]

Intranasal corticosteroids have been increasingly accepted in the control of allergic rhinitis.[2,5,9] Numerous clinical trials have shown that, at recommended dosages, they are a well tolerated and effective modality for the treatment of allergic rhinitis. Although oral corticosteroids are highly effective in the treatment of allergic respiratory disease, they have been associated with serious adverse effects at systemic dosages greater than 10mg of prednisone per day.[10] These adverse effects have been noted to involve all organ systems and

to induce Cushing's Syndrome, obesity, cataracts, suppression of linear growth, osteoporosis and suppression of the hypothalamic-pituitary axis (HPA).[10,11] It was believed that, at therapeutic doses, intranasal corticosteroids did not possess these systemic adverse effects. However, recent data indicate that some systemic absorption does occur.[12-15] The focus of this paper is to review the comparative pharmacology, pharmacokinetics and representative clinical trials of triamcinolone acetonide and other intranasal corticosteroids in an effort to assess the risks and benefits of triamcinolone acetonide use in patients with allergic rhinitis.

The literature reviewed in this article was obtained by performing a search of MEDLINE from 1985 to 1999 using the following key words: nasal corticosteroids, nasal triamcinolone, allergic rhinitis, perennial allergic rhinitis, seasonal allergic rhinitis, nasal mometasone, nasal beclomethasone, nasal fluticasone, nasal flunisolide, nasal budesonide, comparative trials, adverse effects including HPA-axis suppression, growth effects, and long-term safety aspects.

1. Pharmacological Profile of Intranasal Corticosteroids

Topical corticosteroids relieve the symptoms of allergic rhinitis by their anti-inflammatory actions, which include vasoconstriction, suppression of membrane permeability and dampening of the immune response.[7] They primarily affect the late phase of the allergic reaction; significant pretreatment is required before the immediate phase response is affected. Recent data now indicate that there may also be downregulation of the glucocorticoid receptors in the nasal mucosa that occurs after intranasal administration of some corticosteroids.[9] Fluticasone propionate and budesonide have shown this activity.[9] Similar data on other intranasal corticosteroids are not presently available.

Table I. Relative comparability of intranasal corticosteroids (ICS) [from Kelly,[16] with permission]

ICS	Relative lipophilicity	Receptor complex half-life (h)	Receptor-binding affinity[a]	Topical skin blanching potency[b]
TA	3.4	3.9	3.6	330
BEC	4.9	NA	0.4	600
FLU	3.4	3.5	1.8	330
BUD	3.6	5.1	9.4	980
FP	4.5	10.5	18.0	1200
MOM	NA	NA	NA	NA

a Relative binding affinities with dexamethasone equal to 1.

b Relative to dexamethasone equal to 1.

BEC = beclomethasone; **BUD** = budesonide; **FLU** = flunisolide; **FP** = fluticasone propionate; **MOM** = mometasone; **NA** = not available; **TA** = triamcinolone.

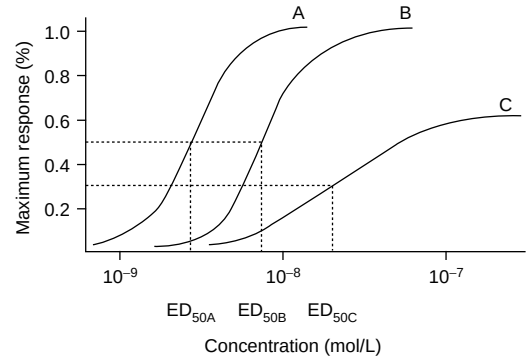

Fig. 1. Concentration-response curves of 3 different drugs in the same pharmacological class. Curves A and B = 2 drugs of equal efficacy but different potencies; curve C = drug with different efficacy and different potency. **ED_{50}** = median effective dose (from Kelly,[16] with permission).

The *in vivo* and *in vitro* pharmacological properties of intranasal corticosteroids are best depicted by receptor binding affinity studies and a non-invasive topical blanching technique, with duration of effect being governed by nasal retention on the basis of lipophilicity and receptor half-life.[16] Available parameters for these indices appear in table I. The variance in potency among the intranasal corticosteroids [fluticasone propionate = mometasone > budesonide = beclomethasone > triamcinolone acetonide = flunisolide] may not always affect efficacy, which is more dependent on what dosages are used in the clinical comparisons.[17,18] For example, the dose-response curve of different agents as seen in figure 1 illustrates that an evaluation of curves A and B at the midpoint of

each curve would provide quite different results than if performed at the top or plateau of the curve. This concept would explain why triamcinolone acetonide with a low potency level at a dosage of 200 μg/day would still provide a similar degree of efficacy as a more potent corticosteroid because the dosage used would be at the plateau of the dose-response curve.

The glucocorticoid receptor affinity and receptor residency time are 2 parameters that govern duration of activity. Although triamcinolone acetonide and budesonide have a lower glucocorticoid receptor affinity and residency time than fluticasone propionate and mometasone, they are still effective when administered once daily.[16,19,20] This may in part be due to the dosage used and to nasal retention, which increases with the aqueous formulation. The intranasal pharmacokinetics of these agents will be further discussed in section 2.

There are various suitable intranasal corticosteroid agents available, including triamcinolone acetonide, beclomethasone, flunisolide, budesonide, fluticasone propionate and mometasone.[7] Triamcinolone acetonide is dispensed by a pressurised spray containing 55 μg/spray in both aqueous and aerosol formulations. Symptomatic relief is noted at 110 to 220 μg/day with the aqueous formulation, and at 110 to 440 μg/day with the aerosol. A greater effectiveness is seen at the higher doses.

Beclomethasone (42 μg/spray) is available as a suspension in a pressurised spray or as an aqueous solution. The normal dose of beclomethasone is 1 spray of the pressurised form or 2 sprays of the aqueous form given twice daily.

Flunisolide is a pump spray with a propylene glycol base. An incidence of nasal stinging and burning of approximately 45% has been noted.[2,7] A change in the formulation (reducing propylene glycol to a 5% concentration with 2.5% polysorbate and increasing polyethylene glycol to 15 to 20%) resulted in a significant reduction of nasal irritation. The normal dose is 2 sprays (25 μg/spray, 1 to 2 sprays in each nostril) twice a day.

Budesonide, fluticasone propionate and mometasone are recent additions to the intranasal corticosteroid group.[21-27] Budesonide is available in both an aqueous and a powder formulation and is to be taken at 256 μg/day, either as 2 sprays twice daily or 4 sprays once daily. Fluticasone propionate is to be taken at 100 to 200 μg/day. Mometasone is available as an aqueous suspension and is taken as 200 μg/day (50 μg/spray, 2 sprays in each nostril).

2. Timecourse of Action and Pharmacokinetic Profile of Triamcinolone Acetonide

The comparative pharmacokinetic parameters for triamcinolone acetonide and other intranasal corticosteroids are presented in table II.[16,28] The time course of action for intranasal corticosteroids will vary with study design and definition of targeted activity. The onset of action profile for triamcinolone acetonide was determined in 85 patients with ragweed-induced allergic rhinitis, provoked with ragweed allergen.[29] Onset was defined as a greater than 25% reduction in nasal congestion from baseline at challenges, and this occurred by 10 hours. After 1 day of treatment, nasal congestion was significantly less in the triamcinolone acetonide group versus placebo: 41 versus 7%, respectively.

The nasal pharmacokinetics of the specific intranasal corticosteroids will govern nasal absorption, retention and relative bioavailability. With the exception of beclomethasone, the intranasal corticosteroids do not undergo a first-pass effect in the nose, so absorption of unchanged drug will go directly into the systemic circulation.[30] However, there will be first-pass metabolism of the swallowed fraction of the dose, which will influence oral bioavailability. The summation of both nasal and oral bioavailability will contribute to overall systemic absorption of the corticosteroid.

Nasal deposition and retention will impact tissue targeting and enhance efficacy in rhinitis. Deposition studies noted that about 4% of the aqueous triamcinolone acetonide 110mg dose was distributed to the maxillary and frontal sinuses within 30 seconds and 64% was distributed to the target tissues (frontal cavity, sinuses and turbinates). Af-

Table II. Pharmacokinetics of intranasal corticosteroids[16,28]

	Triamcinolone	Beclomethasone	Flunisolide[a]	Budesonide	Fluticasone propionate	Mometasone
Absorption						
Absorption (%)	22[b], 25[b]	20[c]	50	10 (oral)	<2 (absolute)	NA
Bioavailability (%)	23[d]	15-20[d]	39[c]	100 (intranasal)	16 (DPI), 30 (MDI)	NA
Distribution						
Volume of distribution (L)	99.5	NA	125[b]	200	258[b]	NA
Protein binding (%)	68[c]	87	NA	88	91	NA
Metabolism and excretion						
Site of metabolism	Lung, kidney	Lung, liver	Liver	Liver (CYP3A)	Liver (CYP3A4)	Liver (extensive)
Metabolites (activity)	6β-hydroxy triamcinolone acetonide, 21-carboxy triamcinolone acetonide and 21-carboxy-6β-hydroxytriamcinolone acetonide (<parent)	17-mono propionate (active), free beclomethasone (very weak anti-inflammatory effects)	6β-hydroxyglucuronide and sulfate conjugates (<parent)	16α-hydroxy prednisolone and 6β-hydroxy budesonide (<1% of parent)	17β-carboxylic acid (negligible in animal studies)	
Excretion site	Urine (≈40%), faeces (≈60%)	Faeces, urine (12-15%)[d]	Urine (≈50%), faeces (≈50%)	Urine (≈67%), faeces	Faeces, urine (<5%)	Urine, small extent metabolism
Elimination half-life (h)	3.1	0.5[b]	1-2	2	3	5.8
Systemic clearance (L/h)	45-69,37	230	58[e]	84[e,f],55[e]	66,NA	NA

a Flunisolide is available as 2 formulations, Nasarel® and Nasalide® which are not bioequilvalent. Total absorption of Nasarel® was 25% less and the peak plasma concentration was 30% lower than Nasalide®.

b Data from inhalation administration.

c Theoretical estimate for inhaled beclomethasone aerosol.

d Data from oral dose.

e Radiolaballed.

f Tube spacer for inhalation.

CYP = cytochrome P450; **DPI** = dry powder inhaler; **MDI** = metered dose inhaler; **< parent** = activity of metabolite greater than parent.

ter 2 hours, 16% was still retained in the target tissues.[19] In the case of the aqueous triamcinolone acetonide formulation, the increased nasal retention will influence nasal bioavailability and simultaneously decrease oral bioavailability and subsequent systemic bioactivity.

Similar pharmacokinetic parameters for triamcinolone acetonide were noted in both allergic and non-allergic volunteers, which suggests that nasal inflammation does not alter the absorption of the aerosol triamcinolone acetonide formulation. After 440 μg/day of the aerosol for 6 weeks, the maximum drug concentration (C_{max}) was 0.40 μg/L and the time to reach C_{max} (t_{max}) was 4.0 hours.[20,31]

In 24 patients with allergic rhinitis and 24 volunteers, the C_{max} values of triamcinolone acetonide were dose dependent and greater for the aqueous formulation at all 3 dosage levels of 110, 220 and 440μg. There was little difference between patients and volunteers. Concentrations and area under the concentration-time curve values were greater with the aqueous than with the aerosol formulation.[19]

The t_{max} for the aerosol formulation was 2.9 and 4.5 hours, and the t_{max} for the aqueous formulation

Table III. Summary of clinical trials of triamcinolone acetonide (TA)

Study	No. of patients (age in years)	Drugs/dosages	Study design/duration	Outcome
Aerosol formulation				
Tinkelman et al.[32]	168 (18-65)	TA 25μg 4 times daily *vs* placebo	Multicentre, double-blind, placebo-controlled, 4-week, SAR study	TA more effective than placebo, well tolerated
Spector et al.[33]	205 (16-65)	TA 200 μg/day given as 4 divided doses *vs* placebo	Multicentre, double-blind, 12-week, PAR study	TA gave significant symptom improvement over placebo
Storms et al.[34]	305 (12-65; adult and paediatric enrolment equal)	TA 110, 220 or 440 μg/day *vs* placebo	Randomised, double-blind, placebo-controlled, parallel groups, 12-week, 1 week baseline PAR and SAR studies	TA 220 and 440 μg/day were more effective in controlling symptoms than placebo. TA was clinically and statistically superior to placebo
Welch et al.[35]	210 (4-12; paediatric study)	TA 82.5 and 165 μg/day given as 3 divided doses *vs* placebo	Placebo-controlled, PAR study	High dose TA showed statistically significant improvement in symptoms compared with placebo. Lower dose TA was marginally effective but not to the level of statistical significance
Aqueous formulation				
Settipane et al.[36]	429 (≥18)	TA 220 μg/day *vs* placebo	Double-blind, placebo-controlled, SAR study	TA showed statistically significant reduced nasal symptoms over placebo
Kobayashi et al.[37]	178 (11-59)	TA 220 μg/day as 1 dose *vs* placebo	Multicentre, randomised, double-blind, placebo-controlled, PAR study	TA showed statistically significant improvement in nasal symptoms over placebo
Munk et al.[38]	140 (20-65; 76 male, 64 female)	TA 220 μg/day *vs* placebo	Multicentre, double-blind, 2-week, SAR study	TA showed greater improvement than placebo
Smith et al.[39]	223 (6-12; paediatric study)	TA 110 and 220 μg/day *vs* placebo	Double-blind, randomised, placebo-controlled, SAR study	TA greater improvement over placebo, well tolerated
Goldberg and Simpson[40]	315 (4-12; paediatric study)	TA 110 and 220 μg/day as 1 dose *vs* placebo	Randomised, double-blind, placebo-controlled, PAR study	TA (both doses) more effective than placebo
Comparisons with antihistamines				
Schoenwetter & Lim[41]	274 (12-70)	TA 220 μg/day *vs* loratadine 10 mg/day	Multicentre, double-blind, randomised, parallel design, SAR study	Greater improvement in all rhinitis symptoms for the TA group over loratadine
Gawchik et al.[42]	305 (adults)	TA intranasal inhaler 220 μg/day as 1 dose *vs* loratadine tablets 10 mg/day as 1 dose	Randomised, double-blind, 4-week, SAR study	TA was more effective than loratadine in relieving symptoms
Comparisons with intranasal corticosteroids				
Van Bavel et al.[43]	120	TA intranasal 220 μg/day *vs* FLU aqueous spray 220 μg/day given as 2 divided doses	Single-blind, randomised, 4-week, PAR study	TA less irritating than FLU in 6 out of 10 variables. TA administration in qid regimen was similar to FLU with few nasal adverse effects
Winder et al.[44]	169 (18-64)	TA 220 μg/day *vs* BEC aqueous spray 168 μg/day	Single-blind, randomised, PAR study	TA showed greater improvement in summated rhinitis symptoms and was rated higher by physicians and patients
Nsouli et al.[45]	16 (adults)	BEC pocket inhaler 83μg bid *vs* TA 110 μg/day	Parallel group design, 12-week study	Allergic rhinitis symptoms decreased 87% in BEC group and 62% in TA group. Both groups showed therapeutic benefits but TA group showed more significant benefits

Table III. Contd

Study	No. of patients (age in years)	Drugs/dosages	Study design/duration	Outcome
LaForce et al.[46]		TA aqueous 220 μg/day *vs* BEC aqueous 336 μg/day given as 2 divided doses	Randomised, double-blind, SAR study	TA comparable to BEC
Small et al.[47]	225 (2-70)	TA 220 μg/day and FP 200 μg/day	Parallel group design, SAR study	Similar improvement with both drugs

BEC = beclomethasone; **bid** = twice daily; **FLU** = flunisolide; **FP** = fluticasone propionate; **PAR** = perennial allergic rhinitis; **qd** = every day; **qid** = 4 times a day; **SAR** = seasonal allergic rhinitis; **tid** = 3 times a day.

was 1.3 to 1.8 hours for patients and volunteers, respectively. Half-life values were shorter for the aqueous product versus the aerosol.[19]

The rapid elimination pharmacokinetic parameters of triamcinolone acetonide (aqueous formulation) will further decrease any systemic bioactivity by way of its rapid elimination from the systemic circulation.

3. Review of Clinical Trials of Triamcinolone Acetonide

Various studies have evaluated aqueous and aerosol triamcinolone acetonide formulations in both perennial allergic rhinitis (PAR) and seasonal allergic rhinitis (SAR) in adults and children. We have reviewed representative studies in both PAR and SAR in an attempt to address both the tolerability and efficacy of triamcinolone acetonide compared with antihistamines and other intranasal corticosteroids as reported in the current literature. Table III tabulates the studies reviewed, and a discussion of these trials follows.

3.1 Triamcinolone Acetonide Aerosol Formulation Trials

Tinkelman and associates[32] reported a multicentre study evaluating 168 patients (aged 18 to 65 years) with SAR in a double-blind, placebo-controlled trial. Patients received 25μg per actuation of triamcinolone acetonide per nostril 4 times daily for 4 weeks. Patients kept a daily diary rating of rhinitis symptoms and global assessments of drug efficacy were made by both the patient and the physician.

Of the 168 evaluable patients, a significant reduction in symptoms were seen at weeks 1 and 2. In the overall study, significant improvement in evaluation ratings for nasal stuffiness, nasal discharge, sneezing, itching of the eyes and tearing or lacrimation ($p < 0.001$) was seen in the group given triamcinolone acetonide. Superiority to placebo was evident as early as day 1 and maintained throughout the study. Patients and physicians both rated triamcinolone acetonide as more effective than placebo ($p < 0.001$). There was a marked reduction in nasal smear eosinophilia in the triamcinolone acetonide group. Evaluations of tolerability revealed no difference between groups, including no evidence of suppression of the adrenal axis and no nasal fungal infection. This study confirmed that triamcinolone acetonide 25μg per nostril 4 times a day is effective and well tolerated.

These results indicated that triamcinolone acetonide is statistically and clinically better than placebo in reducing rhinitis symptoms, nasal stuffiness, nasal discharge, sneezing and itching of the eyes (tearing and/or lacrimation). However, symptom improvement was greatest with regard to nasal stuffiness, nasal discharge and sneezing. This improvement can be attributed to the effect of corticosteroids in suppressing the inflammatory reaction and in inhibiting mediator release. The reduction of symptoms was analysed statistically at the end of the last week of the study. This reduction was maintained throughout the study. The tolerability

of the drug was evaluated by diaries, physical examinations and morning cortisol levels. There was no evidence of HPA axis suppression.

In a multicentre, double-blind study of 205 patients (aged 16 to 65 years) with PAR administered intranasal triamcinolone acetonide aerosol 200 μg/day given in 4 divided doses, Spector et al.[33] demonstrated statistically significant symptomatic improvements over placebo. The primary efficacy variables consisted of nasal stuffiness, nasal discharge, sneezing and nasal index. The greater degree of improvement was statistically significant at 1 week and maintained over the 12-week study period. Another efficacy variable, percentage of nasal eosinophils, was lower in the triamcinolone acetonide group. The adverse effect profile was similar between triamcinolone acetonide and placebo. Triamcinolone acetonide had no effect on serum cortisol levels.

Storms et al.[34] reported a randomised, double-blind, placebo-controlled, parallel group study in 11 centres to evaluate the tolerability and efficacy of a once-daily regimen of 110, 220 or 440 μg/day of intranasal triamcinolone acetonide versus placebo in relieving symptoms of rhinitis in 305 patients over 12 weeks. Patients with a history of PAR for 2 years were included in the study if they had not responded to antihistamines.[34] The study was divided into a baseline period for 7 days followed by a double-blind period of 12 weeks. The ages of the patients ranged from 12 to 65 years; adult and paediatric enrolment was equal. The results showed that the 2 higher doses of triamcinolone acetonide (220 and 440 μg/day) were more effective than placebo in controlling the major symptoms ($p < 0.05$), improvement in sneezing and the nasal index of stuffiness, discharge and sneezing. Intranasal triamcinolone acetonide aerosol was clinically and statistically superior to placebo.

Storms[48] summarises the results of 9 studies in both PAR and SAR conducted at 57 centres. Five were studies in SAR, 3 were studies with PAR and 1 was a dose-response study. The treatment period for the SAR studies was 4 weeks and it was 12 weeks for PAR studies, with dosages ranging from 110 to 440 μg/day. All studies demonstrated statistically significant improvement in symptoms. In addition, some studies demonstrated the efficacy of using once daily administration of triamcinolone acetonide aerosol.

Welch et al.[35] assessed the efficacy and tolerability of 2 dose levels of triamcinolone acetonide in 210 children (4 to 12 years of age) with PAR. The higher dose of 165 μg/day in 3 divided doses showed a statistically significant improvement in rhinitis symptoms in comparison to placebo. The lower dose of 82.5 μg/day was marginally effective, but not to the level of statistical significance. Nasal airflow was improved in a subset of patients with the higher dose. A similar incidence of adverse effects which were minor occurred among all treatment groups. Epistaxis was rare and occurred with the same frequency as the placebo group. There were no significant changes in the morning serum cortisol levels in any group.

3.2 Triamcinolone Acetonide Aqueous Formulation Trials

Settipane et al.[36] and Kobayashi et al.[37] reported studies investigating aqueous triamcinolone acetonide administration in patients with both SAR and PAR. Settipane and associates studied an aqueous triamcinolone acetonide formulation in a double-blind, placebo-controlled study in 429 patients (≥18 years) with ragweed-induced SAR.[36] During the first week of therapy, aqueous triamcinolone acetonide 220 μg/day statistically significantly reduced nasal symptoms compared with placebo. Adverse effects were low (e.g. headache and nasal irritation) and comparable to placebo.

Kobayashi et al.[37] reported a multicentre, randomised, double-blind, placebo-controlled trial evaluating aqueous triamcinolone acetonide 220 μg/day in 178 patients aged between 11 and 59 years with PAR. Aqueous triamcinolone acetonide provided statistically significantly greater improvement in nasal symptoms compared with placebo. Sneezing improved significantly in the first day and the nasal index by the third day. Adverse events were mild between groups; headache was

more common in the placebo group and epistaxis was more frequent in the triamcinolone acetonide group.

Munk et al.[38] evaluated aqueous triamcinolone acetonide in a multicentre, double-blind trial designed to compare the tolerability and efficacy of triamcinolone acetonide with placebo. For a 2-week period, 140 patients (76 males and 64 females) aged between 20 and 65 years were given either placebo or triamcinolone acetonide 220 μg/day. Patients evaluated the severity of seasonal symptoms for 2 weeks according to a 4-point scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe). Physician global evaluations of overall treatment effectiveness were assessed. An improvement in nasal index occurred as early as 12 hours after the first dose of triamcinolone acetonide. Patients receiving triamcinolone acetonide experienced greater improvement ($p < 0.05$) than those administered placebo at weeks 1 and 2. No adverse events were related to the topical effects of the intranasal preparation. The results of this study demonstrated that the aqueous formulation of triamcinolone acetonide was well tolerated and effective in relieving the symptoms of SAR.

Furthermore, Smith et al.[39] reported the effectiveness of once-daily aqueous triamcinolone acetonide 110 and 220 μg/day in 223 children (aged 6 to 12 years) with SAR, while Goldberg and Simpson[40] evaluated aqueous triamcinolone acetonide 110 and 220 μg/day in 315 children (aged 4 to 12 years) with PAR in a double-blind, placebo-controlled study. In the latter study, both dosages of triamcinolone acetonide were superior to placebo.

3.3 Comparative Drug Trials With Antihistamines

Antihistamines have been referred to as the gold standard in the treatment of patients with allergic rhinitis. They are frequently used by patients seeking relief from symptoms and are available over-the-counter. They are used by many physicians out of fear of adverse effects from intranasal corticosteroids. Several clinical trials have selectively looked at comparative effects with specific antihistamines.[2] Antihistamines have been reported to affect cognitive function, which may impact on their use in certain patients.[49] Antihistamines work best if started pre-season and if taken on a daily basis.[2]

Schoenwetter and Lim[41] reported a multicentre, double-blind, randomised, parallel design study comparing intranasal triamcinolone acetonide 220 μg/day and loratadine 10 mg/day in 274 patients (aged 12 to 70 years old) with ragweed-induced allergic rhinitis. There was a statistically significant greater improvement in all rhinitis symptoms for the triamcinolone acetonide group compared with the loratadine group. Both treatment groups had similar adverse event profiles, with headache being the most common adverse effect.

Gawchik et al.[42] evaluated the intranasal aqueous triamcinolone acetonide inhaler 220 μg/day versus loratadine tablets 10 mg/day. These investigators randomised 305 patients with ragweed allergies in a double-blind fashion for 4 weeks. Both triamcinolone acetonide and loratadine recipients had symptomatic relief by as early as day 1. Physician global assessment at the final visit showed a statistically significant difference of 0.002 favouring the triamcinolone acetonide inhaler. Triamcinolone acetonide was more effective than loratadine in relieving rhinitis symptoms in patients with ragweed-induced rhinitis.

3.4 Comparative Drug Trials With Other Intranasal Corticosteroids

Van Bavel et al.[43] compared intranasal triamcinolone acetonide versus flunisolide in patients with PAR in a single-blind, randomised trial. For 4 weeks, 120 patients received either triamcinolone acetonide 220 μg/day or flunisolide 200 μg/day administered in 2 divided doses. Triamcinolone acetonide therapy was less irritating than flunisolide in 6 out of 10 variables. The study demonstrated that triamcinolone acetonide administered in a convenient once-a-day regimen was similar to flunisolide, with few nasal adverse effects.

Winder et al.[44] reported a randomised trial of triamcinolone acetonide and beclomethasone aqueous spray. In a single-blind, randomised trial, 169 patients were given either triamcinolone acetonide 220 μg/day or beclomethasone 168 μg/day administered in 2 divided doses. Triamcinolone acetonide therapy produced a greater improvement in summated rhinitis symptoms and was rated higher by physicians and patients. Evaluation of adverse effects revealed no significant difference between the 2 groups.

Nsouli et al.[45] conducted 2 parallel investigations to compare the clinical efficacy of beclomethasone pocket inhaler (83μg twice daily) versus triamcinolone acetonide (110 μg/day). Each group of 8 patients underwent a 12-week treatment period. Groups were monitored by flexible rhinoscopy and a subjective symptom score. allergic rhinitis symptoms decreased in 7/8 patients (87%) in the beclomethasone group and in 5/8 patients (62%) in the triamcinolone acetonide group. Both groups showed therapeutic benefits, but the triamcinolone acetonide group demonstrated more significant benefits.

In another study, LaForce and colleagues[46] compared aqueous triamcinolone acetonide given once daily to an aqueous beclomethasone formulation given twice daily. This randomised trial demonstrated that triamcinolone acetonide 220μg once daily was comparable to aqueous beclomethasone 336 μg/day given as 2 divided doses for the relief of SAR. Similarly, Small et al.[47] compared triamcinolone acetonide 220 μg/day and fluticasone propionate 200 μg/day for 3 weeks and found comparable improvements in allergic rhinitis symptomatology.

4. Adverse Experiences and Tolerability Profile for Triamcinolone Acetonide and Other Intranasal Corticosteroids

The more common adverse experiences of intranasal corticosteroids are local irritation, epistaxis and headache. There has been a general perception that the intranasal corticosteroids were devoid of systemic effects since they were topically applied to nasal mucosa. However, it is now apparent from recent studies that systemic effects have been detected.[12,13,23,50,51] In some cases, there is up to 100% nasal bioavailability of these agents.[52] Issues of main concern are HPA-axis suppression and effects on growth, particularly in children.

Storms et al.[48] noted that in clinical trials triamcinolone acetonide produced no adrenal suppression at the recommended doses, and Ziemniak[20] reported that 3200μg (64 puffs at 8 times the recommended dose) would produce plasma levels of 3 mg/L. This is the point at which cortisol levels dropped below normal.

Howland et al.[53] evaluated adrenocortical function in 64 male patients with allergic rhinitis who were treated with either 220 or 440μg of aqueous intranasal triamcinolone acetonide spray, 10mg oral prednisone or placebo for 6 weeks. Plasma cortisol levels were obtained before and after treatment using a cosyntropin stimulation test. There were no statistically significant effects on adrenocortical function with either dose of triamcinolone acetonide versus placebo, while prednisone was associated with a significant reduction in the mean 6-hour plasma cortisol level and change from baseline.

HPA axis suppression has occurred with excessive doses of intranasal corticosteroids (beclomethasone dose > 1700μg at 5 times the normal dose; flunisolide at 3 times the normal dose).[7]

Furthermore, Knutsson et al.[12] examined the effect of intranasal budesonide and fluticasone propionate on the adrenal gland at standard doses for 1 week, followed by double doses for the second week. The higher doses were associated with a reduction in urinary cortisol levels, and serum cortisol and osteocalcin values. Wilson et al.[51] compared the effects of intranasal fluticasone propionate 200 μg/day, triamcinolone acetonide 220 μg/day, beclomethasone 336 μg/day and placebo on HPA axis function. Cortisol parameters were reassessed after 4 days of continual administration, and overnight urinary cortisol excretion values were suppressed as follows: 43% by fluticasone propionate, 23% by triamcinolone acetonide and 21% by beclomethasone. Fluticasone propionate was the only agent that demonstrated a statistically

significant suppression. None of the agents showed a blunting of the response to corticotropin (adrenocorticotrophic hormone) stimulation. When assessing these trials, it is important to note whether sensitive diagnostic methods have been employed in making conclusions on these agents.

The growth effects of intranasal corticosteroids are of specific concern in children. A retrospective study in children on daily triamcinolone acetonide administration for 12 months showed no effect on height and weight.[14] Intermediate growth retardation was demonstrated in prepubertal children treated with beclomethasone 336 μg/day over 12 months. There was also a reduction in growth velocity by knemometry following 6 weeks treatment with intranasal budesonide 400 μg/day.[50] In a subsequent study, Wolthers and Pederson[13] investigated the administration of budesonide 200 and 400 μg/day and placebo over a 4-week period. There were no changes at the 200 μg/day level, but at 400 μg/day there was a reduction in mean growth velocity, although not at the level of statistical significance.

5. Pharmacotherapy Advantages of Triamcinolone Acetonide

Triamcinolone acetonide provides an attenuation of the allergic immune response. Triamcinolone acetonide 200 μg/day reduced nasal eosinophilia and albumin levels but had no effect on histamine or tryptase levels.[32-34,54-57] At a dose of 440 μg/day, a reduced response to controlled allergen exposure in both upper and lower airways was noted.[58] In addition, compared with placebo, the 440 μg/day dose reduced nasal ragweed specific IgE and attenuated the seasonal increase in specific IgE. Within 1 day of treatment, a reduction in early phase symptoms was noted.[58]

When compared with prednisone 10 mg/day there was no effect on adrenocortical function in adults with rhinitis after 6 weeks of therapy.[59] Similarly, no effect was seen with the aqueous formulation at a dosage of 220 to 440 μg/day in a noncomparative study in children.[60,61]

It appears that triamcinolone acetonide has fewer effects on growth and HPA axis function than some of the other intranasal corticosteroids, probably because of its lower potency, and intranasal and systemic pharmacokinetics.[19,20,60,61]

6. Benefit Assessment of Triamcinolone Acetonide

Once-daily administration of intranasal triamcinolone acetonide provides effective relief of congestion, rhinorrhoea and sneezing in patients with allergic rhinitis. In addition, symptomatic improvement is observed within 1 day of initial administration and efficacy is maintained throughout therapy. A reduction of symptom scores was noted for 2 weeks after decreasing the dose by half and ocular symptoms were also reduced in patients receiving triamcinolone acetonide.[32]

A comparison of oral triamcinolone acetonide with topical triamcinolone acetonide indicated that treatment is achieved by topical contact. Neither placebo nor oral triamcinolone acetonide improved nasal symptoms. In patients with SAR, those who received triamcinolone acetonide 220 μg/day topically performed better than those who received placebo for at least 1 week before the pollen season.[55,57]

Triamcinolone acetonide produced a similar reduction in baseline symptoms when compared with other intranasally administered corticosteroids, such as aqueous beclomethasone 84, 166 or 168μg twice daily[44-46,62] for 12 weeks, fluticasone propionate 200 μg/day for 3 weeks,[47] and flunisolide 100μg twice daily for 4 weeks.[43] The efficacy of triamcinolone acetonide appears to be comparable with other intranasal corticosteroids in rhinitis, with possibly fewer systemic adverse effects.[7,19,20,48]

Wood and Eggleston[58] observed that intranasal triamcinolone acetonide, when administered at a dose of 110mg per nostril twice daily for 1 week before exposure to cat allergen, reduced both nasal and pulmonary responses to all exposures. The effect was most notable during the first 30 minutes but was negligible at the end of the 1-hour

challenge, indicating that the effects of the drug were overcome by excessive cat allergen exposure. The effect on lower airway response was most noticeable at 30 minutes, but there was no significant difference at 60 minutes which was similar to the nasal response. These results indicated a role for intranasal corticosteroid use in the treatment of cat-induced asthma, and also supported the hypothesis that the control of nasal disease will lead to an improvement of allergen-induced asthma. In addition, anti-inflammatory agents such as triamcinolone acetonide would reduce the risk of secondary rhinovirus infections.[63]

7. Conclusion

Physicians must be continuously aware of the therapeutic options available for the treatment of allergic rhinitis. Awareness of these choices involves a knowledge of the proper use of the available products and their advantages and disadvantages, and also a clear understanding of the potential adverse effects and the patient's overall responsiveness to treatment by addressing quality-of-life concerns.

In the recent International Rhinitis Management Working Group 1994 guidelines,[64] it was recommended that when environmental controls and antihistamines fail, intranasal corticosteroids are the next line of therapy. The Joint Council on Allergy, Asthma and Immunology (AAAAI and ACAAI) also recommends nasal corticosteroids as the most effective medication class in controlling symptoms of allergic rhinitis. In patients with SAR and PAR, intranasal corticosteroids have become the gold standard of treatment.

Clinical trials of triamcinolone acetonide clearly indicate that the benefit ratio far exceeds the risk ratio in treatment trials. The key benefit of the use of triamcinolone acetonide (both aqueous and aerosol formulations) is once-a-day administration. There are minimal systemic adverse effects at the recommended dosages. Adverse events are limited to headache, nasal irritation, and epistaxis from traumatic application of the nozzle. Nasal septal perforation and fungal infection have not been reported with triamcinolone acetonide use.

The response to therapy with triamcinolone acetonide has been observed as early as the first day of treatment. Onset of action has been seen as early as 10 hours, with symptomatic improvement occurring within 3 to 10 days of starting therapy. The key procedure is direct application of the medication to the middle meatus. If this application is obstructed either by polyps, nasal septal deviation, thick mucous secretion or oedema of turbinates, and medication does not get in direct contact with the mucosa, the response will be impaired.

Comparative trials with other intranasal corticosteroids appear to show a similar level of efficacy. There is a slight variance in adverse effects due to the relative potencies and inherent product characteristics.

The major advantage of triamcinolone acetonide use is direct topical application of the agent to the nasal mucosa, the target organ of symptomatology. It is important to keep in mind that the potential for systemic absorption exists when medication is used for prolonged periods at a higher dose, and when the same patient is on inhaled corticosteroids for asthma. In this situation, the cumulative dosage may result in systemic effects. It is therefore helpful to assess all patients at the onset of therapy and at follow-up visits. In addition, a physical examination looking for corticosteroid adverse effects, nasal septal irritation, bleeding and/or perforation, as well as quality-of-life issues should be addressed at each visit.

In long term studies (> 1 year), the major adverse effects were shown to be headache and epistaxis, and one report of oral fungal infection was noted.[35] A retrospective study in children receiving daily triamcinolone acetonide for 12 months showed no effect on height and weight.[65] Caution should also be used in patients who have had recent nasal surgery or who have nasal septal perforation.

The recommended maximum dose of triamcinolone acetonide in adults and children is 220μg once a day. The aerosol form may be recommended in children 7 to 12 years old, in doses up to 440μg

once a day or in divided doses. The duration of allergy treatment is generally for the length of each allergy season. If symptoms are perennial, then a reduction of dosage is made to the lowest effective dose with monitoring every 3 months for risk and benefit assessment.

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