REVIEW ARTICLE

Drug Safety 2003; 26 (12): 863-893
0114-5916/03/0012-0863/$30.00/0

Safety and Tolerability Profiles of Intranasal Antihistamines and Intranasal Corticosteroids in the Treatment of Allergic Rhinitis

Rami Jean Salib and *Peter Hugo Howarth*

Respiratory Cell and Molecular Biology, Faculty of Medicine, Southampton General Hospital, Southampton, United Kingdom

Contents

Abstract

Intranasal corticosteroids and intranasal antihistamines are efficacious topical therapies in the treatment of allergic rhinitis. This review addresses their relative roles in the management of this disease, focusing on their safety and tolerability profiles. The intranasal route of administration delivers drug directly to the target organ, thereby minimising the potential for the systemic adverse effects that may be evident with oral therapy. Furthermore, the topical route of delivery enables the use of lower doses of medication. Such therapies, predominantly available as aqueous formulations following the ban of chlorofluorocarbon propellants, have minimal local adverse effects.

Intranasal application of therapy can induce sneezing in the hyper-reactive nose, and transient local irritation has been described with certain formulations. Intranasal administration of corticosteroids is associated with minor nose bleeding in a small proportion of recipients. This effect has been attributed to the vasoconstrictor activity of the corticosteroid molecules, and is considered to account for the very rare occurrence of nasal septal perforation. Nasal biopsy studies do not show any detrimental structural effects within the nasal mucosa with long-term administration of intranasal corticosteroids. Much attention has focused on the systemic safety of intranasal application. When administered at standard recommended therapeutic dosage, the intranasal antihistamines do not cause significant sedation or impairment of psychomotor function, effects that would be evident when these agents are administered orally at a therapeutically relevant dosage.

The systemic bioavailability of intranasal corticosteroids varies from <1% to up to 40–50% and influences the risk of systemic adverse effects. Because the dose delivered topically is small, this is not a major consideration, and extensive studies have not identified significant effects on the hypothalamic-pituitary--adrenal axis with continued treatment. A small effect on growth has been reported in one study in children receiving a standard dosage over 1 year, however. This has not been found in prospective studies with the intranasal corticosteroids that have low systemic bioavailability and therefore the judicious choice of intranasal formulation, particularly if there is concurrent corticosteroid inhalation for asthma, is prudent. There is no evidence that such considerations are relevant to shorter-term use, such as in intermittent or seasonal disease.

Intranasal therapy, which represents a major mode of drug delivery in allergic rhinitis, thus has a very favourable benefit/risk ratio and is the preferred route of administration for corticosteroids in the treatment of this disease, as well as an important option for antihistaminic therapy, particularly if rapid symptom relief is required.

Allergic rhinitis arises following an initial sensitisation phase, in which allergen presentation results in antibody (IgE) formation and the development of atopy. Subsequently, depending upon the level of exposure and the degree of sensitisation, allergen can then trigger a humoral response, which underlies the clinical disease phase and is manifested by symptoms such as nasal itching, sneezing, rhinorrhoea and nasal obstruction. Allergic rhinitis is a common condition, having increased substantially in prevalence during the 20th century,[1] and now represents a global health problem affecting 10–25% of the world population.[2,3] The socioeconomic impact of allergic rhinitis is considerable, particularly when not only the direct costs of management but also the indirect costs from reduced productivity and absenteeism from work are taken into account. These costs do not include the further expense of treating conditions associated with allergic rhinitis, such as asthma, sinusitis, otitis media, nasal polyposis, lower respiratory tract infection and dental malocclusion.[4]

Previously, based on the timing of exposure, allergic rhinitis was subdivided into seasonal and perennial varieties. Although such a subdivision is relevant in countries such as UK, this is not so in many parts of the world where, because of the nature of the climate, typical seasonal allergens are in fact perennial. It is also recognised that in those patients who are multisensitised to allergens, such as tree, grass and weed pollens, their 'seasonal' disease is prolonged. In the recent document on allergic rhinitis and its impact on asthma (ARIA),[5] the consensus was that this classification was no longer adequate, and therefore a major change was proposed. The new classification based on the ARIA guidelines (table I) subdivides allergic rhinitis, in relation to the duration of the disease, into 'intermittent' or 'persistent' disease. The severity of allergic rhinitis is also classified as 'mild' or 'moderate-severe'.

Intranasal antihistamines and intranasal corticosteroids represent major therapeutic options as first-line medications in the management of allergic rhinitis because of the prominent role of histamine as a mediator of rhinitis and the underlying nature of the allergen-induced airway inflammation, which is glucocorticoid-responsive. Furthermore, topical intranasal therapy allows site-directed treatment with a reduced risk of systemic effects because of the low bioavailability of intranasal antihistamines and intranasal corticosteroids from this site. In blocking the end-organ effects of histamine intranasal antihistamines have a rapid onset of effect and can be used as both 'as required' therapy for intermittent disease relief and as regular daily therapy in persistent disease. In general, the clinical profile of therapeutic benefit with intranasal corticosteroids is greater than with intranasal antihistamines in rhinitis, because of the more widespread effect of intranasal corticosteroids on mucosal inflammation. Since there is a delay before the anti-inflammatory effect is clinically manifested following initiation of therapy, intranasal corticosteroids have, until recently, been predominantly used for the treatment of persistent disease. The debate is still ongoing, however, concerning the safety and tolerability profiles of intranasal antihistamines and intranasal corticosteroids, particularly in relation to the systemic bioavailability of intranasal corticosteroids and their potential to modify growth in children.

This review adopts an evidence-based approach to conduct a thorough critical and comparative analysis of the currently available data, particularly concerning the safety and tolerability profiles of intranasal antihistamines and intranasal corticoster-

Table I. Classification of allergic rhinitis according to ARIA guidelines

Allergic rhinitis	Parameters
Intermittent	Symptoms are present for <4 days per week or for <4 weeks
Persistent	Symptoms are present for >4 days per week and for >4 weeks
Mild	None of the following items are present: sleep disturbance; impairment of daily activities, leisure and/or sport; impairment of school or work; troublesome symptoms
Moderate-severe	One or more of the following items are present: impairment of daily activities, leisure and/or sport; impairment of school or work; troublesome symptoms

ARIA = allergic rhinitis and its impact on asthma.

oids, in the context of their use as topical therapeutic agents in allergic rhinitis.

A computerised literature search of Medline (1966 onwards) and Embase databases was performed using the following search terms: allergic rhinitis, seasonal, perennial, corticosteroids, antihistamines, intranasal or topical, safety, tolerability. In addition, abstracts from key meetings have been included in the search process.

It should be noted, however, that this review is neither meant to be exhaustive, nor is it intended as a systematic review or meta-analysis. Rather it aims to present a balanced perspective, based on the available evidence in the published literature, on the safety and tolerability profiles of intranasal antihistamines and intranasal corticosteroids in the treatment of allergic rhinitis.

1. Intranasal Antihistamines: Historical Perspective

Histamine H_1 receptor antagonists have been the mainstay of therapy for allergic rhinitis since they were first introduced, following the demonstration by Staub and Bovet in 1937 that this class of compounds, newly developed at that time, offers protection against allergen-induced anaphylaxis.[6] Although observational studies reported symptomatic relief in allergic rhinoconjunctivitis with the earliest antihistamines, adverse pharmacological effects, such as sedation, dry mouth, and blurred vision, limited their widespread acceptance. In addition, there was concern that asthma, often associated with rhinitis, could be worsened by antihistaminic therapy,[7,8] although this view is no longer held, nor indeed is it supported by the available evidence.

In general, an ethylamine chain is common to all H_1 receptor antagonists. Many of the additional properties of this class of compounds, with the exception of sedation, can be linked to side-chain radical structure. Structural engineering of these molecules later enabled the synthesis of H_1 receptor antagonists without the anticholinergic,[9] antiserotoninergic,[10] α-adrenergic receptor antagonistic,[11] or local anaesthetic[12] effects evident in earlier compounds. The major breakthrough in the development of H_1 receptor antagonists for clinical use came with the synthesis of the antihistamine, terfenadine, which, while retaining peripheral H_1 receptor antagonist activity, did not appear to cross the blood-brain barrier and was thus devoid of unwanted CNS antihistaminic effects, such as sedation and impairment of psychomotor function.[13] Furthermore, it had no H_2 receptor antagonism, α- or β-adrenergic receptor antagonism, antiserotoninergic or antimuscarinic effects.[14] Thus, in 1981, terfenadine was introduced as the first oral non-sedating antihistamine for the treatment of rhinoconjunctivitis. This represented a major advance in the development of H_1 receptor antagonists for use in the treatment of rhinoconjunctivitis. Other orally administered non-sedating (second-generation) H_1 receptor antagonists were then launched in the 1980s and 1990s. Topical H_1 receptor antagonists such as levocabastine for nasal and ocular administration, azelastine for nasal administration, and more recently emedastine for ocular administration, have subsequently been developed. Topical therapy has the advantage of delivering drug effectively to the target organ while avoiding or minimising systemic adverse effects. Such therapy does have a disadvantage, however, in that if it is not systemically bioavailable, it will modify disease only at that site and not disease concurrently manifesting at other target organ sites. The choice between topical therapy and systemic therapy will thus depend upon the spectrum of disease and the efficacy to safety ratio of therapies.

2. Levocabastine

2.1 General Overview

Levocabastine has been reviewed by Noble and McTavish.[15] Levocabastine is a potent and selective H_1 receptor antagonist with no appreciable affinity *in vitro* for H_2, dopaminergic, adrenergic, serotoninergic, or cholinergic receptors. The recommended nasal dosage for levocabastine is 0.1mg into each nostril twice daily and ocular dose is 0.03mg administered into each eye twice daily.[16] The nasal efficacy of levocabastine has been demonstrated

under challenge conditions.[17,18] It has a rapid onset of action (10–15 minutes) and is effective for up to 12 hours. These findings have been confirmed in the eye using conjunctival challenge.[18,19]

Administered topically, levocabastine is most effective against nasal itching, sneezing, and rhinorrhoea. There are a number of published placebo-controlled trials in seasonal allergic rhinitis,[20,21] but the majority of studies report comparisons with active medications, such as oral H_1 receptor antagonists,[22,23] sodium cromoglycate (cromolyn sodium),[20,24] or intranasal corticosteroids.[22] One placebo-controlled study reported no effect of levocabastine on nasal obstruction in patients with seasonal allergic rhinitis due to mountain cedar, when used at a dosage of 0.2mg twice daily (1 spray into each nostril twice daily), despite clear effects on the neurally-mediated symptoms of itching, sneezing, and rhinorrhoea.[21] Regular therapy with levocabastine is reported to be more effective than a topical antihistamine/decongestant (naphazoline/antazoline) preparation[22] or topical sodium cromoglycate[20,24] in the treatment of allergic rhinoconjunctivitis. A comparative study of levocabastine (0.5 mg/mL, two sprays into each nostril four times daily) and sodium cromoglycate (20 mg/mL, two sprays into each nostril four times daily) involving 114 patients over a 2-week period, found significant symptomatic improvement in allergic rhinitis with levocabastine therapy (76% patients on levocabastine improving vs 46% on sodium cromoglycate).[25] Similar results with more symptom-free days in the levocabastine-treated patients were found in another study.[20] An open observational study comparing efficacy and the onset of action of topical levocabastine nasal spray and eye drops as well as nedocromil nasal spray and eye drops showed that >80% of patients with seasonal allergic rhinitis reported symptom relief with both medications within one hour, amounting to approximately a 50% reduction in symptom severity.[26]

While levocabastine nasal spray has been reported to be as efficacious as topical nasal corticosteroids in allergic rhinitis,[22] the comparative data currently available do not support this view. Intranasal fluticasone propionate was found to be significantly more effective than levocabastine in the treatment of seasonal allergic rhinitis.[27,28] Another study, which assessed nasal nitric oxide levels as a marker of underlying nasal inflammation, reported a significant effect with nasal corticosteroids but not with topical levocabastine.[29] Comparative studies in perennial rhinitis are limited. A preliminary 2-week study reported improvement in sneezing and rhinorrhoea with topical levocabastine compared with placebo, which could not be further improved by the addition of topical nasal beclomethasone dipropionate.[30] Nasal blockage, however, did respond to the additional therapy.

Levocabastine is available as a 0.5 mg/mL microsuspension (0.05% levocabastine hydrochloride) nasal spray and eye drops. The recommended dosage in adults and children >9 years of age is two sprays into each nostril twice daily and one drop into each eye twice daily, both of which could be increased to three to four times daily. Given the renal route of excretion, levocabastine should be used with caution in patients with renal impairment.[31] Dosage recommendations for the elderly population are not currently available. This is a reflection of the relative rarity of allergic rhinitis in this age group.

2.2 Tolerability and Safety Profile

The rationale for the use of a medication for the treatment of a condition is based on assessing the drug's potential for beneficial and adverse effects. The major advantage of the second-generation H_1 receptor antagonists, which significantly improved their benefit/risk profile, was considerably reduced or absent CNS sedative effects when used at standard clinical dosages. Not all new H_1 receptor antagonists, including levocabastine, exhibited this beneficial profile when administered orally. Thus levocabastine, on account of its remarkable potency as an H_1 receptor antagonist, was subsequently developed for topical use. Because of the small volume of delivery, only those H_1 receptor antagonists with reasonable solubility and high potency are suitable for delivery by topical route. Topical therapy minimises the potential for systemic adverse effects

while preserving the therapeutic benefits. Concern that the effect of topical therapy might be limited by rhinorrhoea has not been substantiated. When experimentally-induced rhinorrhoea with methacholine was followed by intranasal levocabastine administration and nasal lavage with saline 30 seconds following intranasal levocabastine administration, there was no evidence of reduction in the efficacy of levocabastine in inhibiting histamine-induced sneezing and rhinorrhoea.[32]

Levocabastine is absorbed following intranasal administration, with systemic bioavailability typically ranging between 60–80% after a single-dose nasal administration,[33] with peak plasma concentration (C_{max}) reached after 1–4 hours.[34,35] C_{max} values of 0.78 μg/L and 1.76 μg/L were reached 2.9 and 4.3 hours following nasal application of 0.1mg and 0.2mg single doses, respectively, in healthy volunteers.[35] Similar values were obtained following repeated administration of levocabastine.[36] In another study, administration of levocabastine nasal spray (0.2mg) to non-atopic volunteers produced a peak plasma concentration range of 1.4–2.2 μg/L.[34] Detailed pharmacokinetic-pharmacodynamic testing has indicated that the clinical benefits evident with levocabastine can be attributed to the local antihistaminic effects at the site of application.[37] Coupled with the fact that levocabastine is subject to minimal hepatic metabolism, a potential site for important drug interactions, these findings suggest theoretically that the likelihood of systemic adverse effects with nasal administration of levocabastine is extremely low. With repeated doses of intranasal levocabastine in healthy volunteers, steady-state plasma concentrations are reached within 7–10 days. The extent of drug absorption appears to be related to the method of administration of topical levocabastine. Conflicting data exist as to the impact of disease on the systemic bioavailability. While higher drug plasma concentrations have been found in healthy non-atopic controls following single dose administration, the opposite effect was noted with multiple dose administration.[34] Following nasal administration, levocabastine is primarily excreted by the kidneys, with an elimination half-life of 35–40 hours.[34] Renal dysfunction may, therefore, be associated with decreased elimination of the drug.[15,31]

The tolerability profile of levocabastine nasal spray has been extensively evaluated in clinical trials. The available data suggest that topical levocabastine is well tolerated, with an adverse effect profile comparable with that of topical sodium cromoglycate and placebo.[21,38-41] A review of the adverse events reported in 1758 patients who received levocabastine nasal spray in clinical trials identified that most common adverse events encountered were headache (4%), nasal irritation (3%), somnolence (3%) and fatigue (2%).[42] None of these occurred more frequently than would have been anticipated with placebo under similar circumstances. In a multicentre, double-blind, placebo-controlled trial evaluating the efficacy and safety of levocabastine nasal spray for seasonal allergic rhinitis, the incidence of adverse events was similar for both the treatment and placebo groups.[21] In this study, most of the adverse events were mild and linked with the disease process, with the most frequently reported being sinusitis (17% in each group), headache (17% with placebo, 14% with levocabastine), and rhinitis (8% with placebo, 2% with levocabastine).[21] This profile of adverse event reporting is similar to that in numerous other clinical trials of topical levocabastine.[23,39-41,43-47] In separate studies, the overall incidence of adverse events has been comparable for levocabastine and placebo (27% vs 31%)[42] and (30% vs 32%).[48] A double-blind parallel-group study (n = 27) comparing the safety and efficacy of topical levocabastine with that of oral terfenadine over an 8-week treatment period, found the incidence of adverse events lower, at 31%, in the levocabastine group compared with 43% in the terfenadine group.[43] Other reports suggest a comparable adverse events profile between topical levocabastine and oral terfenadine (40% versus 41%).[42] To date, there has been no evidence of any clinically significant effect of topical levocabastine on haematological or biochemical parameters. Furthermore, the type and frequency of adverse effects appear to be neither related to the number of daily applications nor increased by the concomitant use of

the eye drops and nasal spray compared with the use of either formulation separately.[42]

Drug safety and tolerability profiles are crucial determinants of therapeutic choices in the paediatric population. A study involving 53 children aged between 6 and 15 years, reported levocabastine to be well tolerated in this age group, with a similar profile of adverse events to that reported in sodium cromoglycate-treated children.[41] The satisfactory paediatric tolerability profile of topical levocabastine has also been confirmed in another study involving 32 children between the ages of 5 and 11 years, who were treated with topical levocabastine over a 20-day period.[49]

2.3 Specific Safety and Tolerability Issues

2.3.1 Local Tolerability

It is well documented that intranasal administration of certain drugs, in particular decongestants, can influence ciliary motility of the upper airways.[50] Although topical administration of levocabastine can be associated with a sense of nasal irritation,[20,38,46] there is no evidence of a clinically significant effect of the drug on ciliary beat frequency or mucociliary clearance.[51] There is no evidence that levocabastine nasal spray causes any significant taste disturbance when used in the treatment of allergic rhinitis.

2.3.2 CNS Effects

Sedation is the most common adverse effect of the first-generation antihistamines because of their capacity to cross the blood-brain barrier. The severity of adverse effect could range from subclinically impaired reaction times to clear sedation. In view of its pharmacokinetic profile, particularly its low plasma concentration following intranasal administration, levocabastine is considered unlikely to be associated with any significant sedative effects.[33] This is supported by findings in specific studies of psychomotor and cognitive function following topical administration of levocabastine.[52,53] One such study investigated potential psychomotor effects of levocabastine (eye drops and nasal spray) following single- and multiple-dose administration, and compared the findings with those of oral triprolidine.[52] Performance was assessed using validated cognitive and psychomotor tests as sensitive measures of the sedative effects of psychoactive drugs. In contrast to the significant sedative effect of triprolidine, topical administration of levocabastine eye drops and nasal spray, at concentrations levels up to 2.0 mg/mL (four times the recommended concentration), had no demonstrable effect on psychomotor function in healthy volunteers.[52] There is no evidence of any pharmacokinetic or psychomotor interactions between intranasal levocabastine and alcohol or diazepam.[42]

2.3.3 Cardiovascular Effects

In vitro and *in vivo* human and animal models have been used to assess the possible cardiovascular effects of levocabastine following oral, ocular and nasal administration. The results have not revealed any demonstrable effects of levocabastine on action potential amplitude, duration, or any other key cardiovascular parameter.[42] Human studies with topically administered levocabastine did not reveal any significant ECG changes. Several studies in healthy volunteers have reported no significant effects on QT or corrected QT (QTc) intervals following treatment with levocabastine in single or repeated doses, even when the nasal spray and eye drops were used in combination four times daily (1.2 mg/day).[38,42]

2.3.4 Drug Interactions

Topical levocabastine administration is unlikely to be associated with any clinically significant drug interactions because of its low plasma concentration and negligible hepatic metabolism. However, the theoretical potential for drug interactions, in the form of binding site displacement, does exist since levocabastine has the ability to bind to plasma proteins, particularly albumin. This risk has not been seen in practice. *In vitro* studies of potential drug interactions have so far failed to show any significant alteration of plasma protein binding of many drugs, including cimetidine and ketoconazole, in relation to the concurrent administration of levocabastine. Small increases (up to 8%) in the proportion of unbound levocabastine have been identified

with certain high protein-bound drugs, such as sulfadimidine (sulfamethazine), tolbutamide and warfarin. This is of little clinical significance for levocabastine, which has a plasma protein binding level of only 55%.[33]

2.3.5 Use in Pregnancy

Topical antihistamines, including levocabastine, have not been shown to have potential teratogenic or embryotoxic effects. Hence, therapeutic use in pregnancy is not currently specifically contraindicated.[54]

2.3.6 Other Effects

There has been no evidence of carcinogenicity or tumour progression in patients taking therapeutic doses of any antihistamine.[55]

3. Azelastine

3.1 General Overview

Azelastine has been reviewed by McNeely and Wiseman.[56] Azelastine, a phthalazinone derivative, is a second-generation H_1 receptor antagonist, but caused sedation when administered orally and thus developed for topical application to the nose.[57] Topical administration via the intranasal route confines the effect largely to the nose and reduces the likelihood of adverse effects due to systemic absorption. Azelastine is selective to H_1 receptors on standard receptor affinity testing and, consistent with this, is clinically efficacious in reducing sneezing, itching and watery rhinorrhoea. In addition to its antihistaminic effect, azelastine has been reported to display additional biological activity compatible with 'anti-allergic' or 'anti-inflammatory' properties. Studies *in vitro* have shown azelastine inhibits both mast cell and basophil activation.[58] It has been proposed that such activity may explain the reports that topical nasal therapy with azelastine reduces nasal obstruction in addition to the classical histamine-mediated neural symptoms. Azelastine, administered as a nasal spray, has been found to be more effective than oral azelastine or terfenadine in relieving nasal obstruction, while producing comparable relief of other nasal symptoms.[59] Consistent with this suggestion, in a nasal allergen challenge study, Ciprandi and colleagues found that daily treatment with topical azelastine for 1 week before challenge reduced the allergen-induced epithelial expression of intercellular adhesion molecule-1 (ICAM-1) during the early and late phase reactions, as well as reducing the late phase eosinophil and neutrophil recruitment.[60] The same group have also identified that topical azelastine reduces the epithelial expression of ICAM-1 in naturally-occurring seasonal allergic rhinitis, with a more consistent effect with regular than on demand therapy.[61] A number of other antihistamines have also been shown to modify epithelial ICAM-1 expression; however, it is unclear as to whether this represents an additional biological activity or is purely a reflection of H_1 receptor blockade. Integral to the dilemma over the *in vivo* antiallergic activity of topical azelastine is the failure of this therapy to modify cell recruitment within the nose in naturally-occurring seasonal allergic rhinitis.[62] Thus, despite a number of clinical studies showing a reduction in nasal obstruction with azelastine,[56,63,64] there exists no consensus to date regarding the mechanism, particularly as not all studies have demonstrated this beneficial effect.[65,66]

Standard dosage of topical azelastine is 0.14mg into each nostril twice daily. While in one study half the standard daily dosage (0.28 mg/day) was found to be as effective as the standard dosage (0.56 mg/day) in improving symptoms, the benefit of the standard dose was reflected by a significantly greater use of rescue medication in the lower dosage treatment group.[61] Symptomatic improvement is reported as early as 30 minutes following the intranasal administration of azelastine, in a high-dose treatment regimen (two puffs into each nostril [0.56 mg]), and is apparent for up to 12 hours in patients with seasonal allergic rhinitis.[56] There have been a number of placebo-controlled trials of azelastine in allergic rhinitis. One such trial involving a 6-week study of azelastine nasal spray (0.14mg into each nostril twice daily; total dosage 0.56mg) in children with perennial allergic rhinitis reported a beneficial effect compared with placebo on all nasal symp-

toms, including nasal obstruction.[67] The clinical efficacy of azelastine nasal spray has also been demonstrated in the treatment of vasomotor (perennial non-allergic) rhinitis.[68,69] Other studies have focused on comparisons in seasonal and perennial allergic rhinitis with other active medications, such as antihistamines[63,66] and nasal corticosteroids.[62,70-75]

While azelastine nasal spray has been reported to be as efficacious as topical nasal corticosteroids, such comparative studies are limited and further studies are required before valid comparisons can be made. One study involving seasonal allergic rhinitis patients receiving nasal corticosteroids or oral antihistamines who remained symptomatic after a 1- to 2-week washout period, compared double-dose azelastine (1.1 mg/day) with the combination of loratadine (10mg daily) and nasal beclomethasone (336 μg/day).[70] Following one week of treatment, no statistical difference was evident between the treatments, and it was concluded that azelastine was as effective as the combination therapy with loratadine and beclomethasone.[70] However, caution has to be exercised when interpreting results of such a study, as the effect of the nasal corticosteroid is unlikely to have been fully expressed within the time frame of the study. Therefore, this study essentially might have represented a basic comparison of azelastine and loratadine. Intranasal azelastine (one puff into each nostril twice daily) is generally as effective as standard therapeutic doses of other antihistamines, including intranasal levocabastine[76] and oral cetirizine,[77,78] ebastine,[79] loratadine[80] and terfenadine[81] in achieving symptomatic improvement in patients with allergic rhinitis.

Azelastine nasal spray is available as a 1 mg/mL solution of azelastine hydrochloride in a metered dose pump spray bottle (0.14 mg/metered spray). The US prescribing recommendations specify two puffs into each nostril twice daily for adults and children aged ≥12 years. In the UK and a number of other European countries, however, azelastine is recommended as one spray into each nostril twice daily for adults and children ≥5 years.[82]

3.2 Tolerability and Safety Profile

There is a paucity of peer-reviewed publications on pharmacokinetic properties of intranasal azelastine. Following 29 days of intranasal azelastine at a dosage of 0.56 mg/day, a maximum plasma concentration of 0.306 μg/L was achieved approximately 2.5 hours after administration.[59,83,84] The mean steady-state plasma concentration of intranasal azelastine was 0.26 μg/L in healthy volunteers compared with 0.65 μg/L in patients. The equivalent figure for oral azelastine 4.4 mg/day assessed after 29 days was 8.02 μg/L. The estimated systemic exposure to the intranasal drug was 6- to 8-fold lower than that with oral azelastine.[85-87] A systemic bioavailability of 40% has been shown following intranasal azelastine administration.[84] Unfortunately, the recipient group (i.e. whether patients or healthy volunteers) in the study was not defined. Azelastine is metabolised by the cytochrome P450 enzyme system to its major active metabolite, desmethylazelastine. At steady-state, the plasma metabolite concentration accounts for 20–50% of the azelastine concentration.[88] No data are currently available on the elimination half-life of intranasal azelastine.[56]

Topical antihistamines, such as azelastine, have the specific advantage of delivering high concentrations of the drug more effectively into the target organ while avoiding or minimising systemic adverse effects. In postmarketing surveys, including a total of 7682 patients between the ages of 3 and 85 years who were treated with intranasal azelastine (one spray into each nostril twice daily) for a period of 14 days or 31 days, the most common adverse effects reported by 4002 of the patients 31 days post-treatment included rhinitis (4%), taste disturbance (2.5%) and nasal irritation (1.2%).[89] Other effects including somnolence, dry mouth, epistaxis and headache occurred in <1% of patients. With intranasal azelastine administration as monotherapy in one study, 8% of patients reported adverse events. This figure rose to 20% when intranasal azelastine was combined with other oral antihistamines and/or topical nasal corticosteroids.[90]

Azelastine is generally well tolerated in clinical trials, with a physician and/or patient global assessment of tolerability (where stated) of at least 'good' in >70% of patients (adults and children aged ≥7 years) receiving intranasal azelastine (one puff into each nostril twice daily).[73,77,79,81,91] Good tolerability of azelastine is also generally evident in clinical trials of up to 6 months' duration,[91] with long-term studies also confirming this. For example, one study with intranasal azelastine in 35 patients over a period of 21 months reported that >90% of the participants rated the tolerability of the medication as at least 'good'.[92] The most frequently reported adverse events associated with the use of intranasal azelastine included taste disturbance,[65,66,71,73,93,94] and nasal irritation.[72,76,79,95] The taste disturbance, often short lasting,[63,95] was associated with the drug trickling down the throat, rather than a systemic adverse effect.[65,66,93]

Azelastine appears to be well tolerated in the paediatric population as well. In a study involving 62 children treated with azelastine (0.56 mg/day for 6 months),[91] the most frequently reported adverse events were sneezing (16%), nasal itching (11%), bitter taste (11%) and nasal dryness (9.6%).The tolerability was rated as at least 'good' by the investigators in 74% of participants.[91]

Treatment withdrawal due to azelastine-related adverse events was infrequent, occurring in ≤7% of patients receiving therapy (range of 1–3 patients per study). Reasons for withdrawal included nasal itchiness, congestion, nausea, vomiting, dizziness and hypertension.[64,72,78,80] In clinical trials, the overall tolerability of intranasal azelastine was comparable with that of oral cetirizine,[77,78] intranasal budesonide,[73,74] and intranasal levocabastine.[76]

3.3 Specific Safety and Tolerability Issues

3.3.1 CNS Effects

To date, there have been no formal objective studies investigating the effect of topical azelastine on the CNS in humans. However, animal studies have not shown azelastine to have any significant effect on spontaneous electroencephalogram activity or the susceptibility of the ascending reticular activating system.[55,96] Although sedation secondary to treatment with intranasal azelastine has been reported in some studies, its incidence was not significantly different when compared with placebo controls.[65,66,93,95] When compared with other oral H_1 receptor antagonists such as ebastine[79] and cetirizine,[77] azelastine was associated with significantly less incidence of sedation. In addition the results of some studies have even suggested that intranasal azelastine improved overall alertness and vigilance.[71,90,97,98] It has been suggested that somnolence may be a feature of the rhinitis rather than the treatment. Nevertheless, since some patients in clinical trials have reported somnolence, the US prescribing recommendations include a warning regarding the concurrent use of such medication and driving or operating potentially dangerous machinery. Concurrent use of alcohol and/or other CNS suppressants is not recommended because of possible potentiation of the sedative effect.[88]

3.3.2 Cardiovascular Effects

Cardiac adverse effects, including serious ventricular arrhythmias that can be fatal, have been described for the second-generation oral H_1 receptor antagonists terfenadine and astemizole. However, this is not a class effect and depends on their ability to interfere with the potassium rectifier current in the heart with consequent prolongation of the QTc interval on the ECG.[99] These risks are present only when these agents are either taken in overdosage, or in the presence of impaired liver function, or with the concomitant administration of compounds that compete with the enzyme cytochrome P450, such as macrolides (e.g. erythromycin) and azolic antifungals (e.g. ketoconazole), which results in an increase in the plasma levels of terfenadine and astemizole. A similar effect has also been noted during concomitant ingestion of grapefruit juice.[100] No such adverse events have been reported with azelastine, although there is a paucity of peer-reviewed literature on this aspect. One abstract reported that in a double-blind trial, in which perennial rhinitis patients were randomised to receive azelastine (two puffs per nostril) or placebo twice daily for 8 weeks, no significant changes were found in the following

parameters: mean heart rate or blood pressure, or PR, QS, QT or QT_c intervals on ECG.[101] Age did not appear to influence any of the results. No specific interactions have been reported between intranasal azelastine and oral erythromycin or ketoconazole.[88,102]

3.3.3 Use in Pregnancy

There are no data to support any association between azelastine administration in pregnancy and the incidence of congenital malformations. Therefore, the use of topical azelastine is not specifically contraindicated during pregnancy.[54]

3.3.4 Other Effects

No evidence exists of carcinogenicity or tumour progression in patients taking antihistamines of any form.[55]

4. Intranasal Corticosteroids

4.1 General Overview

Beclomethasone, the first topical corticosteroid for the treatment of seasonal allergic rhinitis, was introduced in 1973 as a nasal spray.[103] Over the following two decades, several other intranasal corticosteroids have been developed and marketed. These include budesonide, flunisolide, fluticasone propionate, mometasone, triamcinolone, and more recently ciclesonide.[5] The commercial availability of these products is very much country-dependent.

The introduction of intranasal corticosteroids represented a revolutionary concept at the time in that it substantially enhanced the therapeutic and safety profiles of these agents because these could be administered topically. The rationale for using intranasal corticosteroids in the treatment of allergic rhinitis was that high drug concentrations could be achieved at receptor sites in the nasal mucosa, with only a minimal risk of systemic adverse effects.[5] At the molecular level, corticosteroids mediate their effect by binding to a single glucocorticoid receptor (GR), which is predominantly localised to the cytoplasm of target cells. The effect on inflammatory cells is mediated via the activation of this GR, which, following translocation to the nucleus, either promotes or inhibits gene transcription through processes known as transactivation and transrepression, respectively.[104] Through this activity, corticosteroids exert anti-inflammatory effects by influencing cytokine and mediator release, thereby modifying inflammatory cell recruitment within target organs, such as the nose. intranasal corticosteroids reduce cell recruitment within the nose and reduce the epithelial accumulation of mast cells, eosinophils and antigen presenting cells, through modifying endothelial and epithelial cell activation. This anti-inflammatory effect underlies the identification of reduced levels of mediators, such as histamine, tryptase, prostanoids, and leukotrienes in nasal lavage fluid after treatment with nasal corticosteroids in allergic rhinitis. Topical therapy with intranasal corticosteroids has also been shown to inhibit the seasonal increase in serum levels of circulating pollen-specific IgE antibodies.[5] It is this widespread effect on various stages of the allergic inflammatory process that underlies their efficacy in allergic rhinitis.

Intranasal corticosteroids are currently recognised as the most potent and effective topical medication available for the treatment of allergic rhinitis, and their superior efficacy in treating this condition has been substantiated in many clinical trials. In three international reports on the management of allergic rhinitis, intranasal corticosteroids were considered as the first-line therapeutic choice for adults with moderate to severe seasonal or perennial allergic rhinitis.[105-107] The regular prophylactic use of intranasal corticosteroids is effective in reducing nasal blockage, rhinorrhoea, sneezing and nasal itching in adults and children with seasonal and perennial allergic rhinitis.[5] A meta-analysis has shown that intranasal corticosteroids are more efficacious than oral H_1 receptor antagonists in reducing the symptoms of allergic rhinitis, with the advantage being most obvious for nasal blockage.[108] A superior clinical efficacy has also been established for intranasal corticosteroids compared with intranasal H_1 receptor antagonists[109] and intranasal sodium cromoglycate.[110,111] Intranasal corticosteroids are equally effective in patients with seasonal or perennial allergic rhinitis. Although small differ-

ences exist in some trials, current evidence does not support any significant overall differences in efficacy between different intranasal corticosteroids when they are administered at dosages adjusted for their differing potencies.[112] The prominent effect of intranasal corticosteroids on nasal blockage, in conjunction with their anti-inflammatory properties,[107] makes them stand out among other available treatments, especially in perennial rhinitis and chronic disease states in which nasal obstruction is a particular problem. It has also been reported that intranasal corticosteroids, even when applied topically to the nose, have effects comparable with oral H_1 receptor antagonists in modifying conjunctivitis in seasonal allergic disease,[108] and may also modify disease expression within the lower airways, with reports of a beneficial effect on both bronchial hyper-responsiveness and symptoms in coexisting asthma.[113-118] The majority of these effects, however, are associated with intranasal beclomethasone. Beclomethasone may differ from some other intranasal corticosteroids in its systemic bioavailability (*vide infra*) therefore, it is uncertain whether these extranasal effects reflect disease modification within the nasal mucosa influencing disease at other sites, or alternatively, represent a direct systemic effect of intranasally administered treatment.

Although intranasal corticosteroids are considered to have a slower onset of action than H_1 receptor antagonists (≥12 hours), maximum efficacy tends to develop over a period of days and weeks.[119-121] Intranasal corticosteroids should be taken regularly in seasonal allergic rhinitis,[122] and, in patients in whom quality of life had been adversely affected in previous years, treatment should ideally be commenced prior to the start of the pollen season for maximal effect.[107] A once-daily regimen is normally sufficient in most cases and is associated with good patient compliance.[123-125] Twice-daily administration may be indicated in severe cases and during exacerbations. The recent ARIA document[5] recommends intranasal corticosteroids as first-line treatment in moderate-to-severe allergic rhinitis. With intermittent symptoms in mild persistent disease, H_1 receptor antagonists are a reasonable choice, either an H_1-antihistamine or an intranasal corticosteroid is recommended as first-line therapeutic option, with the additional consideration of a step up to an intranasal corticosteroid if an H_1-antihistamine is first selected and later found to inadequately control symptoms.[5] The common clinical practice of combining intranasal corticosteroids and oral antihistamines in the treatment of allergic rhinitis is not supported by clinical evidence. Since the combination does not appear to increase the efficacy beyond that of an intranasal corticosteroid used alone,[112,126] therefore, can not be justified as a cost-effective option. It is thought that, *in vivo*, the anti-inflammatory effects of intranasal corticosteroids on the upper airway may encompass the effects of the H_1 receptor antagonists, making the effect of the latter insignificant.

Most of the intranasal corticosteroids formulations nowadays are administered via mechanical aqueous pump sprays or as dry powder, with effective and safe delivery systems. The choice of formulation is dependent on the patient's personal preference.[5]

4.2 Pharmacokinetic Considerations

The pharmacokinetic consideration with a topical therapy in allergic rhinitis is its potential for systemic bioavailability following nasal administration, a process dependent upon factors such as the properties of the pharmacological molecule, its mode of delivery, the influence of the disease state, and the fate of the absorbed molecule once within the circulation, which will be influenced by factors such as its volume of distribution, metabolism and excretion profiles. The net potential of any agent will depend upon the balance between these factors. When only one factor is focused on, e.g. drug potency or drug lipophilicity, there may be a misapprehension as to the likelihood of systemic adverse effects from an intranasally administered corticosteroid. However, since intranasal administration is an important route of systemic absorption that bypasses the protective effects of first-pass metabolism, consideration of the factors affecting systemic bioavailability has assumed greater significance over the past decade,

particularly with the increased availability of newer and more potent topical corticosteroids. In the absence of a change in any other determinant, an increase in potency to achieve an enhanced therapeutic benefit could also be paralleled by an increased potential for systemic adverse effects. It is essential, therefore, to be aware of the pharmacokinetic properties of the different intranasal corticosteroids and their potential for systemic effects, in addition to how the newer drugs compare with the older ones.

Each nasal cavity has a volume of approximately 10mL and the combined nasal mucosal surface area of both nasal cavities for drug absorption is about 180cm2. The physicochemical properties of a drug that determine its absorptive properties from this site include its molecular weight, lipophilicity and particle size. There is an inverse relationship between molecular weight and rate of absorption, with those molecules with a molecular weight of <300 kDa being significantly less influenced by their physicochemical properties and more readily absorbed, while those with >1000 kDa exhibit little absorption. Apart from ciclesonide, which is a prodrug with a molecular weight of 260 kDa, all the other intranasal corticosteroids have molecular weights that range between 430–530 kDa, with the following rank order: budesonide (430.5 kDa), flunisolide (434.5 kDa), triamcinolone (434.5 kDa), fluticasone propionate (500.6kDa), beclomethasone (521.25 kDa), mometasone (521.4 kDa). Thus, there is little difference in the molecular weights of these corticosteroids, and this factor is not crucial in determining differences between their absorption profiles. Although lipophilicity is an important determinant of the ability of a molecule to cross an epithelial barrier, it also determines the tissue retention of the molecule. Fluticasone propionate, which has a high lipophilicity, has been found to exhibit the highest epithelial tissue concentration after *in vitro* incubation in a comparison with budesonide, flunisolide and beclomethasone-17-monopropionate.[127] Metabolism within the tissue site will modify the fraction available for systemic bioavailability and thus any potential for systemic adverse effects. Budesonide undergoes nasal metabolism, in that it is esterified within the nasal tissue, forming pharmacologically inactive, intracellular fatty acid, oleate and palmitate esters.[128] Budesonide is, however, released from these esters by the action of lipases, so this metabolism allows budesonide to have a more prolonged tissue residency than would be anticipated from its lipophilicity profile, but does not bar the drug from eventual bioavailability. The presence of cytochrome P450 isoenzymes within the nasal mucosa may account for the lower bioavailability of both fluticasone propionate and mometasone from this site *(vide infra*) than would be anticipated on the basis of lipophilicity profiles alone, as both these corticosteroids are converted to inactive metabolites in the presence of these enzymes. The hepatic metabolism by these enzymes accounts for the first-pass metabolism of these particular corticosteroids that prevents their systemic bioavailability by the oral route.

The type of delivery device for nasal administration has also been shown to influence the potential for systemic bioavailability. Pressurised metered dose inhalers (pMDIs), aqueous pump sprays and a powder inhaler have been used to topically administer nasal corticosteroids. The aerosol generated from a pMDI has a high velocity and is highly directional, resulting in a narrow proximal deposition in the nasal cavity.[129] Comparatively, the aerosol from an aqueous pump spray displays a large droplet size with a more dispersed pattern of deposition.[130] The nasal distribution pattern with a powder inhaler lies somewhere between the other two devices.[131] A study investigating the systemic availability of various formulations of intranasal budesonide[132] showed a significantly higher absorption level with the aqueous pump spray compared with the pMDI and powder formulations. Following the Montreal agreement, pMDIs are no longer used for nasal administration because of the CFC propellant, and aqueous nasal spray is now the recommended standard delivery device in the treatment of allergic rhinitis. An additional delivery mode, nasal drops, are licensed for use in nasal polyposis and have been used off-label by allergists and rhinologists for the

treatment of severe rhinosinusitis as an alternative to low-dose prednisolone therapy, particularly following endoscopic sinus surgery. These formulations contain higher doses of corticosteroid than are used with nasal spray administration and have caused concern as to their potential for systemic adverse effects, although this is a lesser consideration if they are being used in a situation in which oral prednisolone would otherwise be given. One such formulation is fluticasone propionate nasal drops, Flixonase Nasule®[1], which is licensed for use in Europe at a dose of up to 1600μg daily. It is currently not licensed for use in the US. A recent study investigating the systemic bioavailability of fluticasone propionate administered either as nasal drops or as an aqueous nasal spray formulation, using a sensitive analytical method and a high dose regimen, found that both formulations exhibited low systemic bioavailability, even at 12 times the normal daily dosage.[133] Interestingly, the bioavailability of fluticasone propionate nasal drop formulation (0.06%) was approximately eight times lower that that of the nasal spray (0.51%), which may be explained by the findings that nasal drops are cleared more quickly from the nose than nasal sprays.[134,135]

Another consideration is whether the inflammatory disease process itself has any effect on the absorption of the drug from the nose. It might be anticipated that an inflamed nasal mucosa, with an impaired epithelial barrier, might permit greater systemic absorption than the normal nasal mucosa. Thus, nasal bioavailability studies undertaken in healthy volunteers may not reflect the situation in allergic rhinitis, and may underestimate the potential for nasally administered corticosteroids to produce systemic adverse effects. However, the available evidence to date suggests otherwise. A study investigating the effects of acute and chronic intranasal administration of therapeutic doses of triamcinolone to subjects with active allergic rhinitis, found no significant effect of the nasal mucosal inflammation on the absorption of intranasal triamcinolone.[136] A further study investigating the nasal absorption of desmopressin found no difference between those with house dust mite perennial allergic rhinitis and healthy controls, leading to the conclusion that nasal absorption is unaffected by the disease state in allergic rhinitis.[137] Thus, there is seems no basis for the added concern in allergic rhinitis as to the potential for topical nasal corticosteroids to induce systemic adverse effects.

Once absorbed, the corticosteroids will be distributed within the body fat in relationship to their lipophilicity and will be in equilibrium with the blood, so that as clearance takes place from the blood there will be clearance from the tissue. The greater volume of distribution of the most lipophilic corticosteroids, such as fluticasone propionate and mometasone, has been put forward as a potential risk factor for systemic adverse effects, with the suggestion that the low plasma concentrations with these corticosteroids after intranasal administration gives a false representation of their true systemic bioavailability.[138] This argument is neither supported by the more recent work on urinary cortisol measurements with intranasal mometasone administration,[139] nor by analysis of previous data involving fluticasone propionate in comparison with triamcinolone, when the results are appropriately corrected for urinary creatinine.[140] Indeed, this argument does not stand up to critical appraisal on theoretical grounds, even in the absence of these findings. Despite fluticasone propionate being more lipophilic and having a higher volume of distribution (318L) than the less lipophilic triamcinolone (103L), both of these values are still greatly in excess of the blood volume (5L) and, at steady-state, approximately 98% of fluticasone propionate and 95% of triamcinolone will be in the tissue. With the published bioavailability data for fluticasone propionate and triamcinolone of 0.5% and 46% respectively, at steady-state with standard dosage this would lead to respective tissue doses of 0.7μg and 46μg. Although it will take longer to clear fluticasone propionate than triamcinolone from the tissue once treatment stops, because of the longer half-life of fluticasone, this is irrelevant, as for a substantial period the tissue concentrations of triamcinolone

1 Use of the registered name is for identification purposes only and does not imply endorsement.

will remain in excess of fluticasone propionate because of the because of the higher starting level. Thus, despite lipophilicity being a determinant of tissue concentrations, it does not necessarily follow that more lipophilic corticosteroids have a greater potential for adverse effects. This is because there are other factors, including the percentage of administered drug that is available for systemic delivery, which determine the systemic adverse potential of intranasal corticosteroid due to the activation of tissue GRs. Prior to predicting the potential for newer corticosteroids to induce adverse systemic effects, it is therefore necessary to have access to all such information in order to make an informed judgement.

4.3 Tolerability and Safety Profile

4.3.1 Local Effects

Currently available intranasal corticosteroids are generally well tolerated. Occasional local adverse effects include irritation of the nose and throat, and sneezing bouts because of localised irritation from nasal administration, particularly at the start of the treatment.[141] Other potential adverse effects include crusting, transient dryness, minor epistaxis and, rarely, ulceration.[121,125,142-144] These tend to be self-limiting, but are occasionally persistent, and a change to a different formulation or delivery system may be needed in order to eliminate them. The risk of a septal perforation, albeit minimal, is significant considering the serious implications associated with this. The risk of a perforation appears maximal during the first year of treatment, with mostly young females being affected. The risk is compounded by a history of previous nasal surgery, or erroneous application methods, particularly when the spray or drops are directed towards the nasal septum. It is good practice for prescribing clinicians to advise patients to aim the spray well away from the midline.[145,146] The risk of developing atrophic rhinitis has not been proved.[121] Contact allergic reactions of the skin and mucosa to intranasal corticosteroids are rare, but have been described.[147,148]

4.3.2 Effects on Hypothalamic-Pituitary Adrenal Axis and Growth

The basic principle in measuring the potential systemic bioactivity of corticosteroids is to evaluate a biomarker of an activity that is influenced by exogenous corticosteroid administration, such as suppression of endogenous cortisol secretion from the adrenal cortex.[149] There are currently two basic types of measurements. The first relates to the basal adrenocortical secretion, while the second represents a measure of the dynamic function of the hypothalamic-pituitary adrenal (HPA) axis in order to establish the level of adrenal reserve. Although measurement of the basal levels of adrenocortical secretion is fairly simple in principle, it does possess some inherent disadvantages, particularly in relation to the underlying variation in secretion levels due to the normal circadian rhythm (highest in the morning and lowest around midnight). Thus, variable sampling times could potentially lead to high variability in results and a reduced sensitivity of the test. Nevertheless, this test remains a very simple and relatively reliable method as long as the sampling time is standardised.[138] The most sensitive methods for measurement of basal adrenocortical function are those that integrate either 24-hour or overnight cortisol output as reflected by urinary measurements on samples collected over this time period. This integrated approach towards measurement is very important, particularly as corticosteroids with different pharmacokinetic properties can affect the HPA axis at differing time points during the dosing interval.[138]

The interpretation of dynamic function tests of adrenocortical activity needs to be evaluated within the context of the stimulating dose of corticotropin (adrenocorticotropic hormone). This is because the frequently used dose of corticotropin (250μg) represents a supraphysiological dose that can render the test less sensitive.[138] It is generally accepted that lower doses of corticotropin (0.5–1μg) are as effective in producing a stimulated cortisol response and tend to improve the sensitivity of the test.[150] There are also other issues that need to be considered, particularly when interpreting the results of these types of studies. These include, the issue of whether

the study drug was administered for long enough to reach steady-state levels, issues pertaining to the dosage (e.g. recommended vs higher than licensed dosage), characteristics of the study population (e.g. healthy volunteers vs patients with allergic rhinitis), state of activity (e.g. sedentary vs normal day activity study), duration and timing of the urine collection period (e.g. 12-hour vs <12-hour collection period), method of cortisol assay (e.g. radioimmunoassay vs liquid chromatography tandem mass spectrometry), method of statistical analysis of results (e.g. use of conventional vs unconventional statistical tests), and, importantly, whether the study was adequately powered. The latter consideration is particularly important when comparisons are made between active therapies. It is understandably essential that these and other limitations are considered in determining the validity and strength of any conclusions. Although the influence of intranasal therapy on the HPA axis is the evaluation most often used for determining the bioavailability of systemic corticosteroids, other evaluations on bone turnover with osteocalcin, or bone growth with knemometry, have also been employed.

There is still concern that the continued and, in some cases, prolonged use of intranasal corticosteroids may be associated with systemic adverse effects, including suppression of the HPA axis and an effect on growth. This complicates the use of oral and, in some cases, inhaled corticosteroids for the treatment of asthma. Certainly, the introduction of intranasal formulations has reassured, but has not completely dispelled these fears. For instance, dexamethasone spray and betamethasone drops can rarely provoke systemic effects.[151-155] Additionally, the dosage at which clinically relevant systemic adverse events occur remains controversial.[156,157]

A small number of studies have suggested significant effects of intranasal corticosteroids on the HPA axis.[158,159] Despite such isolated studies, the overwhelming clinical and pharmacokinetic evidence in the published literature to date clearly supports the view that intranasal corticosteroids are unlikely to cause any significant suppression of the HPA axis when administered short-term at the recommended therapeutic dosage.[121,140,160-164] Patients exclusively receiving intranasal corticosteroids appear to be at a very low risk of developing HPA axis suppression because of a number of important factors, including the extensive hepatic first-pass metabolism, limited systemic drug availability and the low dosage.[165-167] This is particularly the case with the newer intranasal corticosteroids, including fluticasone propionate, budesonide, triamcinolone and mometasone, which do not appear to have any significant effects on the HPA axis.[121,140,158,162-164,168-171] The addition of intranasal corticosteroids to inhaled corticosteroids does not appear to increase suppression of the HPA axis.[172] It is important to bear in mind that the apparent lack of HPA axis suppression with intranasal corticosteroids does not preclude the occurrence of other systemic adverse effects, particularly as this endpoint may not be the most sensitive index of systemic bioavailability. The risk of such effects is very much dependent on the systemic bioavailability of the corticosteroid used. This can vary widely, by up to 100-fold in some cases, depending on the topical corticosteroid used.[173]

Two studies have described an effect on children's growth relating to intranasal beclomethasone and budesonide administration.[174,175] These studies did not necessarily indicate a class-specific effect, however, as there were important differences between the varying intranasal preparations and their systemic bioavailability with intranasal application. At the time of these studies, however, there was limited prospective information and, as a precaution, the FDA felt it appropriate to recommend that all intranasal corticosteroids within the US were labelled with a warning that their use in children may adversely affect growth. Beclomethasone has the highest gastrointestinal absorption of the corticosteroids used in the treatment of asthma (relevant on account of the high proportion of swallowed drug from metered dose administration) and, as a nasal corticosteroid, has a bioavailability of 44%,[176] second only to triamcinolone in the currently available intranasal spray preparations. An effect on growth, albeit small, is thus likely to be a reflection

of systemic bioavailability with intranasal beclomethasone when it is administered at its standard recommended dosage for a prolonged period (one year in this study).[174] Budesonide has a lower systemic bioavailability, and the report of an effect of intranasal budesonide on growth stemmed from the administration of the adult dose of 200μg twice daily. Moreover, this result could not be reproduced in another study investigating the effect of budesonide 400μg daily on child growth assessed by lower leg knemometry.[177] Compared with placebo, the study failed to find any inhibitory effect on the short-term growth rate of the children involved. The situation with budesonide is thus not so clearcut. More prospective data is urgently required to further evaluate the safety profile of intranasal corticosteroids in young children.[157] The current recommendation of the Committee on Safety of Medicines in the UK is that the height of children receiving prolonged treatment with nasal corticosteroids should be monitored. If growth appears to be inhibited or slowed, then a paediatric referral should be considered.[82]

The newer topical corticosteroids, such as mometasone and fluticasone propionate, have a substantially reduced systemic bioavailability (<1%), particularly when administered nasally, compared with some of the older corticosteroids, such as beclomethasone and budesonide. Prospective studies with mometasone and fluticasone propionate have not identified any adverse effect on growth when used at standard doses in children.[178] Consequently, the potential for systemic effects can be substantially reduced by careful selection of the intranasal corticosteroid.[176,178,179]

4.3.3 Other Systemic Effects

Smell and taste disturbances and hypersensitivity reactions, including bronchospasm, have been reported to rarely occur.[82] Although adverse effects such as dermal atrophy, cataract formation, glaucoma, metabolic changes, and behavioural abnormalities have been reported in patients receiving corticosteroids administered via other routes, there are no reports to date that link such effects to corticosteroids administered solely via the nasal route.[156]

4.3.4 Use in Pregnancy

There are currently no data to substantiate any association between intranasal corticosteroids and congenital malformations. Inhaled corticosteroids such as beclomethasone or budesonide[180] are not thought to have potential teratogenic or embryotoxic effects, and are used widely by pregnant women with asthma. Although the choice of agents should be based on evidence of fetal safety, the issues of efficacy and maternal health also need to be considered in order to optimise any management plan.[110]

5. Specific Corticosteroids

5.1 Beclomethasone

Beclomethasone has been reviewed by Edelman and van Os.[181] It has a slow gastrointestinal absorption and a rapid first-pass inactivation by the liver.[182] The absolute bioavailability of intranasal beclomethasone is 44%.[176,183] Intranasal dosage of up to 400 μg/day of beclomethasone have not been associated with suppression of the HPA axis when given for up to 6 months.[166,182] However, when used at twice the recommended therapeutic maximal dosage (800 μg/day), beclomethasone was found to reduce urinary cortisol.[184] Despite not having any significant effect on the HPA axis, 12 months' treatment with beclomethasone (mean dose 168μg twice daily) was reported to exert a small but significant ($p < 0.01$) effect on the growth of 6- to 9-year-old children with a mean growth velocity of 4.78 cm/year compared with 6.11 cm/year for the placebo group. This difference of 1.33 cm/year was found to be statistically significant ($p < 0.01$).[185]

A small case series has demonstrated a low incidence of cataracts related to the use of inhaled and intranasal beclomethasone.[186] This case series included 21 spontaneous reports of posterior subcapsular cataracts in patients receiving either intranasal or inhaled corticosteroids. Nine patients were also receiving systemic corticosteroids, which could have influenced the risk of developing cataracts. There were also limitations in this study pertaining to the paucity of details provided, particularly in relation to the dosage and duration of therapy. A

further large-scale observational cohort study of patients aged <70 years, showed the incidence of cataracts following intranasal beclomethasone use was 1/1000 person-years,[187] similar to the incidence rate in the nonusers. However, recipients of oral corticosteroids were at a higher risk of cataract (2.2/1000 person-years). In the UK register of spontaneously reported adverse drug reactions, two cases of cataract associated with the use of intranasal beclomethasone have been reported, representing 0.56% of all reports of cataracts in the UK.[157] For cataract and intranasal corticosteroids, the proportional reporting ratio (PRR) was 5 with a χ^2 of 6.39 ($p < 0.0115$). Despite the significant PRR, the evidence presented overall in the literature certainly does not currently support an association between intranasal corticosteroids and an increased risk of developing cataracts. The raised PRR is probably indicative of a theoretical risk particularly with prolonged high dose therapy.[157] Further studies are required to substantiate these findings.

A large case-controlled study of elderly patients receiving either beclomethasone or fluticasone propionate, did not find an increased risk of developing raised intraocular pressure or low-angle glaucoma.[188] This applied to both low-to-medium doses and high doses of the inhaled corticosteroids. According to manufacturer's data on file only 25 cases of glaucoma/raised intraocular pressure were reported in patients treated with intranasal beclomethasone between 1975 and 1996.[189]

Intranasal beclomethasone has not been found to have a detrimental effect on nasal mucosa or physiology. Rhinoscopic and histopathological examination of the nasal mucosa after 12 months of treatment with intranasal beclomethasone did not reveal any evidence of adverse effects.[190] Electron microscopic analysis of 142 nasal biopsies showed no detrimental effect on the nasal mucosa following 9–36 months of treatment with intranasal beclomethasone (400 μg/day).[191] Septal perforation is a rare complication following the use of intranasal beclomethasone. This has been confirmed in literature reviews.[142,182] According to manufacturer's data on file only 70 cases of septal perforation were reported following the use of intranasal beclomethasone between 1974 and 1996.[189]

The use of intranasal beclomethasone during pregnancy and lactation is not advised by the manufacturer as no prospective studies have been undertaken under such circumstances.[192] A record linkage study has suggested, however, that the rate of congenital malformations in women exposed to beclomethasone during the first trimester does not exceed background rates.[54] The Beconase® patient information leaflet for the non-prescription product advises the consumer to seek advice from their doctor prior to using intranasal beclomethasone during pregnancy.[193]

The local adverse effects associated with intranasal beclomethasone are minimal and include dryness/irritation of nose and throat, unpleasant taste and smell, headache and minor epistaxis. Rare cases of raised intraocular pressure or glaucoma have been reported in association with intranasal beclomethasone administration. The overall reporting frequency for adverse events is very low (approximately 0.18 events per estimated 1000 patient-years).[189,192] There have been no reported incidences of overdose with intranasal beclomethasone. However, it has been shown that at a dosage of 8 mg/day, intranasal beclomethasone did have an effect on the HPA axis in some but not all subjects, with a return to normality after 48 hours.[194] No other local or systemic adverse effects have been reported to date.[5]

5.2 Budesonide

Budesonide aqueous nasal spray has a systemic bioavailability level of 31%.[176] In an open 12-month study, intranasal budesonide used in the treatment of vasomotor (perennial non-allergic) rhinitis at a dose of 400 μg/day did not lead to any significant changes in haematological, biochemical or plasma cortisol levels.[195] The long-term safety and tolerability of intranasal budesonide (200–400 μg/day) has been substantiated over a 12-month period, in which it was not found to cause either nasal mucosal atrophy or suppression of the HPA axis.[196] In a study lasting up to 5.5 years, the

continued use of budesonide nasal aerosol had no measurable effect on the HPA axis and did not alter the nasal epithelium.[197] At a daily dosage of 200μg, intranasal budesonide has not been found to have an effect on the HPA axis.[140,158] One multidose study did report a reduction in urinary cortisol with the use of intranasal budesonide at a daily dosage of 200–800μg.[184] Using knemometry, it was shown that 4-week treatment with intranasal budesonide (200–400 μg/day) did not significantly affect growth velocity, although a trend toward reduction was seen with the 400 μg/day dosage.[176] However, in another study comparing terfenadine (60 mg/day), intranasal budesonide 200 μg/day, and depot methylprednisolone 60mg, a significant reduction in growth velocity was observed over a 6-week period in those children receiving the nasal and systemic corticosteroids.[198] No other local or systemic adverse effects have been reported to date.[5]

5.3 Ciclesonide

Ciclesonide is a new, non-halogenated topical corticosteroid with anti-inflammatory properties,[199] that has recently been found to be effective in the treatment of allergic rhinitis (dose of 200μg into each nostril), and has displayed excellent local and systemic tolerability profiles.[200] A recent placebo-controlled, randomised, double-blind study assessed the influence of inhaled ciclesonide on the circadian time serum cortisol rhythm, and concluded that at a daily dosage of 800μg for 7 days, inhaled ciclesonide did not exert any significant effects on the HPA axis.[201] The systemic bioavailability of intranasal ciclesonide is currently unknown. There have been no reports of systemic adverse effects related to the use of topical ciclesonide to date.

5.4 Flunisolide

Flunisolide aqueous nasal spray has a systemic bioavailability level of 40–50%.[202] No effects of intranasal flunisolide on the HPA axis or growth have been reported to date. A recent 1-year trial evaluating the safety profile of flunisolide hydrofluoroalkane in children with asthma reported no adverse effects associated with HPA axis function, including linear growth in 6- to 11-year-old children, when compared with beclomethasone and sodium cromoglycate.[203] The excipients, polyethylene glycol and polypropylene glycol, can cause transient local irritation manifesting as a stinging sensation.[5] No other local or systemic adverse effects have been reported to date.[5]

5.5 Fluticasone Propionate

The pharmacokinetic profile of intranasal fluticasone propionate minimises the potential for systemic adverse effects. It is estimated that the major portion of the dose is cleared by the nasal cilia and eventually swallowed.[204] Fluticasone propionate aqueous nasal spray has a systemic bioavailability of 0.42–0.51%.[133,176] In view of the low systemic bioavailability and the low therapeutic doses used, there is a low risk of developing suppression of the HPA axis. Although the findings in one study in healthy volunteers suggested that intranasal fluticasone propionate administration was associated with a clinically significant suppression of urinary cortisol,[158] this has not been reported by extensive studies in patient populations (see section 4.2 for a more detailed discussion concerning intranasal corticosteroid bioavailability, particularly in relation to fluticasone propionate). The effects of intranasal fluticasone propionate on HPA axis function were investigated by analysis of morning plasma cortisol concentrations, response to corticotropin and 24-hour urinary free-cortisol excretion.[205] There was no evidence of effects on adrenal function, even at high doses of intranasal fluticasone propionate. Other studies have not found intranasal fluticasone propionate to have an effect on the HPA axis at a daily dose of 200μg in adults[115,164,178,206] or children.[169,207] The overwhelming evidence in the literature regarding the short-term intranasal use of therapeutic doses of intranasal fluticasone propionate certainly backs its clinical safety in that respect.[208] Intranasal fluticasone propionate has not been found to have a significant effect on growth. A study comparing intranasal fluticasone propionate treatment with placebo showed the two groups to be comparable in terms of longitudinal leg growth in a

2-week study in children using knemometry.[209] Inhaled fluticasone propionate has not been shown to have any adverse effects on the growth of children in studies over a period of 12 months.[210]

Intranasal fluticasone propionate use has not been associated with any ocular adverse effects. A large case-controlled study of elderly patients using either beclomethasone or fluticasone propionate did not find an increased risk of developing raised intraocular pressure or low-angle glaucoma.[188] This applied to both low-to-medium doses and high doses of the inhaled corticosteroids. There was no evidence of posterior subcapsular cataracts or glaucoma in patients treated for 1 year with intranasal fluticasone propionate at a dose of 200 μg/day.[208]

There has been one report in the literature of a possible link between intranasal fluticasone propionate administration and the onset of benign intracranial hypertension in a 13-year-old boy.[211] However, it must be stressed that this was an isolated report with poor adherence to the strict diagnostic criteria for this condition. To date, a cause-effect link has yet to be firmly established.

There is no evidence of intranasal fluticasone propionate having any detrimental effect on the nasal mucosa or physiology. Nasal biopsies performed following 12 months of treatment with intranasal fluticasone propionate (200 μg/day) did not reveal any abnormalities on histopathological examination.[121,212] There has recently been controversy regarding the possible ciliostatic effect of benzalkonium chloride, a preservative used in many nasal sprays, on human nasal epithelium *in vivo*. A single-centre, double-blind nasal biopsy study in 22 patients receiving intranasal fluticasone propionate containing benzalkonium chloride, using scanning and transmission electron microscopy examination, found no evidence of such an effect of benzalkonium chloride *in vivo*, when it was applied for 6 weeks (with/without fluticasone propionate) to the nasal mucosa of patients with perennial allergic rhinitis.[213] Intranasal fluticasone propionate has also been shown to have no detrimental effect on nasal physiological parameters following 12 months of treatment at a dose of 200 μg/day.[214] The incidence of septal perforation associated with intranasal fluticasone propionate use is rare, except in the presence of other predisposing factors.[215]

The use of intranasal fluticasone propionate during pregnancy and lactation is not advised by the manufacturer as no prospective studies have been undertaken under such circumstances. There is thus inadequate evidence currently on the safety profile of fluticasone propionate in human pregnancy. In animal reproduction studies, adverse effects typical of potent corticosteroids are only seen following high systemic exposure levels. In the case of direct intranasal application, minimal systemic exposure is ensured.[216,217] The consumer is advised to seek advice from their doctor prior to using intranasal fluticasone propionate during pregnancy.

Considering the very low plasma concentration of fluticasone propionate following intranasal application, clinically significant drug interactions are unlikely.[218] Fluticasone propionate is metabolised by the cytochrome P450 enzyme CYP3A4 to an inactive carboxylic acid metabolite. Therefore, care should be taken when co-administering known strong CYP3A4 inhibitors (e.g. ritonavir or ketoconazole), as there is potential for interaction and subsequent increased risk of systemic adverse effects of fluticasone propionate.[218]

A few local adverse effects have been linked with the use of intranasal fluticasone propionate. These are probably related to the nasal spray itself rather than any active ingredients, and include dryness/irritation of the nose and throat, unpleasant taste and smell, headache, and minor epistaxis. The overall reporting frequency for adverse events is very low, with 0.02% of individuals who have received fluticasone propionate experiencing an adverse event.[216]

There have been few reported incidences of intranasal fluticasone propionate overdose. According to a report from the manufacturer, there were five cases of overdose from 13.1 million patient-years of exposure were reported between March 1998 and August 2001.[219] Incidentally, intranasal fluticasone propionate administered at 20 times the recommended dosage (2mg twice daily) for 7 days, in healthy

adult volunteers, showed no adverse effect on the HPA axis.[204] No other local or systemic adverse effects have been reported to date.[5]

5.6 Mometasone

Mometasone aqueous nasal spray has a systemic bioavailability of 0.46%.[176] In a crossover controlled study,[140] 5-day courses of intranasal mometasone at a clinically recommended dosage (200 μg/day) did not have any significant effect on the HPA axis, bone metabolism or basic haematological parameters. This was confirmed by the results of two further studies.[166,220] Over a 1-year period, treatment of children with perennial rhinitis with intranasal mometasone (100 μg/day) did not appear to suppress the HPA axis or have any inhibitory effect on their short-term growth rate.[178] These findings were paralleled by the results of another study, which failed to detect any effect on the HPA axis in children treated with intranasal mometasone (50, 100, and 200 μg/day) for 7 days.[221] A dose-ranging study of intranasal mometasone in children with seasonal allergic rhinitis concluded that at a dosage of up to 200 μg/day, intranasal mometasone was well tolerated with no significant effects on the HPA axis.[222] The satisfactory safety profile of intranasal mometasone in adults and children with allergic rhinitis has been recently reiterated in reviews[160,223] of the most recent and relevant clinical trials concerning this issue.

A study of adult patients with perennial rhinitis treated for 12 months with intranasal mometasone (200 μg/day) showed no adverse tissue changes in nasal biopsies following treatment.[224] Similarly, no significant effect of intranasal mometasone (200 μg/day) on olfactory function or mucociliary clearance could be detected.[225]

No other local or systemic adverse effects have been reported to date.[5]

5.7 Triamcinolone

Despite having a systemic bioavailability of 46%,[176] intranasal triamcinolone does not appear to cause suppression of the HPA axis. The possible systemic effects of intranasal triamcinolone (110 or 200 μg/day) aqueous nasal spray on the HPA axis were assessed in a study of male subjects with allergic rhinitis.[162] Morning plasma cortisol levels, urinary cortisol, and corticotropin stimulation were evaluated. No significant effect of the nasal corticosteroid on these parameters was found. In another study, no significant changes of morning serum cortisol levels were recorded in 93 patients with allergic rhinitis taking intranasal triamcinolone (110, 220, and 440 μg/day) for >1 year.[226] This finding was further confirmed in one long-term[227] and three medium-term[228-230] studies in adult patients. In a further crossover controlled study,[140] 5-day courses of intranasal triamcinolone at clinically recommended doses did not affect the HPA axis, bone metabolism, or basic haematological parameters. A study conducted in healthy volunteers after a 4-day course of intranasal triamcinolone (220 μg/day) did not report any significant change in overnight urinary cortisol levels.[184] No effect of intranasal triamcinolone was found on serum cortisol or the stimulated corticotropin response in another study.[158] The lack of effect on HPA axis was also established in a study in children.[161] The safety of once-daily administration of intranasal triamcinolone (220 μg/day) for 3 weeks was evaluated in 429 patients with seasonal allergic rhinitis compared with a placebo group.[231] The results showed no significant difference between the two groups. Similar results were obtained in another study.[163] In perennial allergic rhinitis, a multicentre study evaluating the safety of once-daily regimen of intranasal triamcinolone (110, 220, and 440 μg/day) in patients aged between 12 and 65 years demonstrated a satisfactory profile.[232]

Clinical and pathological studies have also been carried out to investigate the long-term effects of intranasal triamcinolone on the nasal epithelium. One such study was a long-term prospective local safety study evaluating the endoscopic and histological changes in the nasal epithelium after a 6-month treatment period with intranasal triamcinolone.[233,234] Results were also compared with those seen with cetirizine and beclomethasone dipropionate. Overall, the results indicated that

long-term intranasal triamcinolone treatment did not result in atrophic changes in the epithelium or impairment of mucociliary function. No other local or systemic adverse effects have been reported to date.[5]

6. Specific Safety and Tolerability Considerations

6.1 Paediatric Population

Although the principles of pharmacological treatment are identical to those in adults, caution has to be exercised in order to avoid adverse events typical in the paediatric population.[107,235] Dosage adaptation and special terms are often necessary, not only because of the age factor, but also to ensure that optimum therapeutic efficacy is achieved.[236,237]

Although often trivialised by parents and doctors, allergic rhinitis is a significant cause of morbidity in the paediatric population, leading to social embarrassment on account of the rhinitis, and on account of the widespread mucosal inflammation affecting several target organs, and a generalised sense of malaise with cognitive function impairment. This can be further compounded by inappropriate antihistamine treatment.[238] For rhinoconjunctivitis in children, intranasal corticosteroids remain the most effective treatment currently available. Although there is a theoretical risk of systemic adverse effects, this has not been shown in practice, particularly with the modern intranasal corticosteroids which have low bioavailability (<30%) with little evidence of significant systemic absorption. It is fairly self-evident that the minimal dose of intranasal corticosteroids should be used when control of symptoms is required. In contrast to the clear inhibitory effect upon growth and growth velocity of oral and depot corticosteroid preparations,[198] the overwhelming evidence does not support a similar effect relating to intranasal corticosteroids administration.[177,178] As previously discussed in section 4.3.2, two studies with intranasal beclomethasone[174] and intranasal budesonide[175] did report inhibitory effects on growth. With this in mind, it is generally agreed nowadays that intranasal corticosteroids with high systemic bioavailability should not be recommended for use in children.[153]

With their action mainly centred on the target organ, and in conjunction with lack of any associated significant systemic effects, the use of intranasal antihistamines, such as levocabastine and azelastine, is clearly advantageous in children. However, despite being safe and useful for relieving nasal/ocular symptoms of allergic rhinitis, the intranasal antihistamines lack the degree of efficacy achieved by intranasal corticosteroids and are thus more appropriate for the treatment of mild or intermittent forms of allergic rhinitis in children, especially where nasal obstruction is not a prominent symptom.[5,20]

6.2 Pregnancy

Allergic rhinitis affects around one-third of women of child bearing age,[54] and is often aggravated by pregnancy.[239-241] Caution must be exercised when prescribing medications to pregnant women, particularly in relation to the potential risk of congenital malformations. A satisfactory safety and tolerability profile in adults does not necessarily rule out such effects in a fetus. Therefore, it is vital when prescribing in pregnancy to consider the benefit/risk ratio for the fetus as well as the mother.[5] Conversely, it must be stressed that in studies pertaining to the possible teratogenic and embryotoxic effects of medications, consideration of the needs of the symptomatic mother for treatments that adequately control the disease, should not be overlooked. Treatment in pregnancy is thus a balance of risk against efficacy, with the balance tilted in favour of safety. Fortunately, topical therapy for the nose has made available an effective treatment modality associated with a minimal risk of systemic adverse effects.

With respect to inhaled corticosteroids, there have been no documented prospective epidemiological studies on their use during pregnancy, but they are frequently used by pregnant women with asthma and have not as yet been incriminated as teratogens.[54] No maternal-fetal adverse effects were

reported in 40 pregnant women with asthma who were treated with beclomethasone.[242]

Although some first-generation antihistamines (e.g. brompheniramine, promethazine, diphenydramine and hydroxyzine) have been shown to be teratogenic in animals,[243,244] there is no evidence for any such effects in humans.[245] Second-generation intranasal antihistamines have not so far been incriminated as human teratogens or embryotoxins and their use during pregnancy is currently not specifically contraindicated.[54]

6.3 The Elderly

Intranasal corticosteroids and topical second-generation antihistamines are fairly well tolerated in the elderly with minimal adverse effects.[5]

7. Conclusion

Taking into account the results of the studies undertaken on intranasal antihistamines and intranasal corticosteroids, it is generally agreed, nowadays, that intranasal corticosteroids are more potent and efficacious in reducing the symptoms of allergic rhinitis than intranasal antihistamines,[246,247] with the particular advantage being most obvious for nasal obstruction.[108,112] The superior efficacy of intranasal corticosteroids is not only evident clinically, but also when one considers other objective parameters, such as inflammatory markers, rhinomanometry, acoustic rhinometry, and quality-of-life assessments.[112,126]

While there exist clear differences in the degree of therapeutic efficacy when intranasal corticosteroids and intranasal antihistamines are compared, no such trend can be identified in the safety/tolerability profiles of these two classes of drugs. Apart from minor qualitative differences in the nature of localised adverse events linked to intranasal corticosteroids (e.g. nasal bleeding) and intranasal antihistamines (e.g. sedation), no significant quantitative discrepancies between the two groups have been found. This is mainly due to a generally low incidence of adverse effects in both treatments.[112] Concern has emerged over the possible effects of intranasal corticosteroids on the HPA axis and growth velocity, however, this risk has not consistently been seen in practice in patients with allergic rhinitis

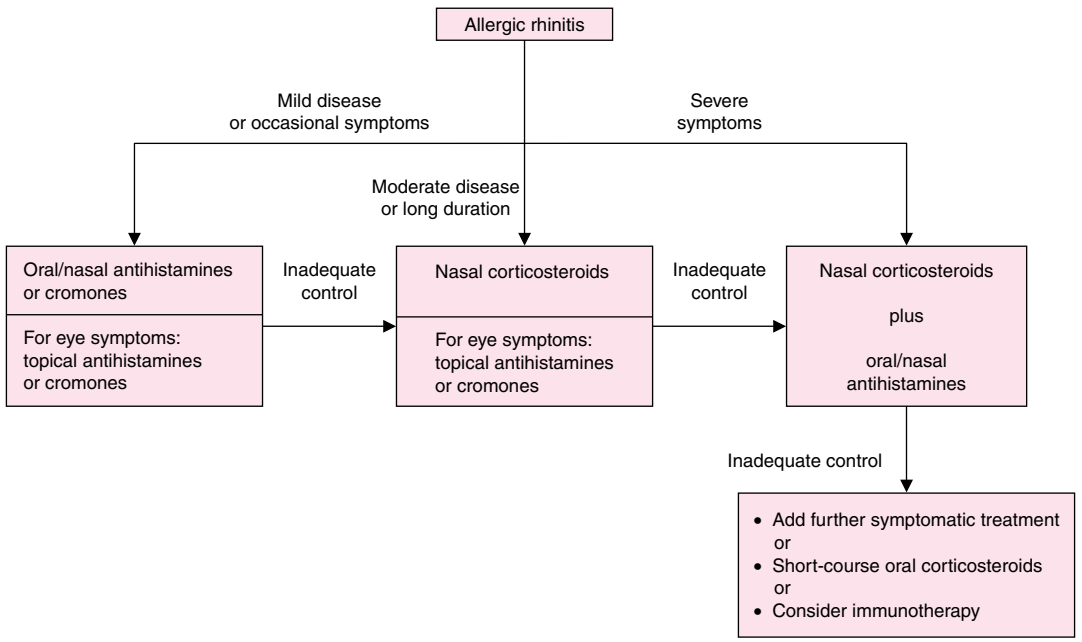

Fig. 1. Algorithm of the management protocol for allergic rhinitis based on the allergic rhinitis and its impact on asthma (ARIA) guidelines.

alone,[28,206,248,249] although only a few studies have prospectively assessed this. The emerging evidence indicates that there may be a small risk with prolonged use with certain nasal corticosteroids. However, the more recently introduced nasal corticosteroids have a substantially reduced systemic bioavailability profile and as such negate this concern. Furthermore, in children and asthmatic patients requiring inhaled corticosteroids, careful selection of the intranasal corticosteroid in conjunction with their use at the lowest possible doses, will significantly reduce the potential for any systemic effects.[176,179]

The current consensus of opinion, as has been expressed in the recent ARIA document,[5] recommends topical antihistamine therapy for mild persistent organ-limited disease or as an on-demand medication for intermittent disease. Intranasal corticosteroids are now accepted as the gold standard therapeutic choice in allergic rhinitis,[250] and as such are recommended as highly effective first-line treatment for patients with allergic rhinitis with moderate-to-severe and/or persistent symptoms (figure 1).[5,105-107,112] In practice, however, the balance between the two agents should be tailored to the individual needs of the patient. There is no evidence that combining intranasal corticosteroids and intranasal antihistamines provides any additional therapeutic benefit to intranasal corticosteroids alone.[112,126] Furthermore, the recent intriguing evidence that 'as required' treatment with an intranasal corticosteroid is more effective than 'as required' oral antihistamines, has yet to be confirmed and assimilated into mainstream practice.[251]

Acknowledgements

This work was supported by a research grant from the Royal College of Surgeons of England. There are no potential conflicts of interest directly relevant to the content of this review.

References

1. Aberg N, Sundell J, Eriksson B, et al. Prevalence of allergic diseases in schoolchildren in relation to family history, upper respiratory infections, and residential characteristics. Allergy 1996; 51 (4): 232-7
2. Sibbald B. Epidemiology of allergic rhinitis. In: Burr ML, editor. Epidemiology of clinical allergy. Monographs in allergy. Basel: Karger, 1993; 31: 61-9
3. Strachan D, Sibbald B, Weiland S, et al. Worldwide variations in prevalence of symptoms of allergic rhinoconjunctivitis in children: the International Study of Asthma and Allergies in Childhood (ISAAC). Pediatr Allergy Immunol 1997; 8 (4): 161-76
4. Spector SL. Overview of comorbid associations of allergic rhinitis. J Allergy Clin Immunol 1997; 99 (2): S773-80
5. Bousquet J, Van Cauwenberge P, Khaltaev N, et al. Allergic rhinitis and its impact on asthma. J Allergy Clin Immunol 2001; 108 (5 Suppl.): S147-334
6. Staub AM, Bovet D. Action de la thymoxyethyldiethylamine (929F) et des ethers phenoliques sur le choc anaphylactique. CR Soc Biol Fil 1937; 125: 818-21
7. Levy L, Seabury JH. Spirometric evaluations of Benadryl in asthma. J Allergy 1947; 18: 244-50
8. Herxheimer H. Antihistamines in bronchial asthma. BMJ 1949; 2: 901-5
9. Pandit PR, Kulkarni SD, Joglekar GV. Study of relationship between antihistaminic, anticholinergic and central depressant properties of various antihistaminics. Indian J Med Sci 1973; 27 (12): 920-4
10. Stone CA, Wenger H, Ludden CT, et al. Antiserotonin-antihistaminic properties of cyroheptadine. J Pharmacol Exp Ther 1961; 131: 73-84
11. Byck R. Drugs and the treatment of psychiatric disorders. In: Goodman LS, Gilman A, editors. The pharmacological basis of therapeutics. New York: McMillan, 1975: 152-200
12. Casterline CL, Evans R. Further studies on the mechanism of human histamine-induced asthma: the effect of an aerosolized H1 receptor antagonist (diphenhydramine). J Allergy Clin Immunol 1977; 59 (6): 420-4
13. Moser L, Huther KJ, Koch-Weser J, et al. Effects of terfenadine and diphenhydramine alone or in combination with diazepam or alcohol on psychomotor performance and subjective feelings. Eur J Clin Pharmacol 1978; 14 (6): 417-23
14. Cheng HC, Woodward JK. Antihistaminic effect of terfenadine: a new piperidine-type-antihistamine. Drug Dev Res 1982; 2: 181-96
15. Noble S, McTavish D. Levocabastine: an update of its pharmacology, clinical efficacy and tolerability in the topical treatment of allergic rhinitis and conjunctivitis. Drugs 1995; 50 (6): 1032-49
16. Howarth PH. Antihistamines in rhinoconjunctivitis. In: Simons E, editor. Histamines and H1-antihistamines in allergic diseases. New York: Marcel Dekker Inc, 2002: 179-220
17. Holmberg K, Pipkorn U, Bake B, et al. Effects of topical treatment with H1 and H2 antagonists on clinical symptoms and nasal vascular reactions in patients with allergic rhinitis. Allergy 1989; 44 (4): 281-7
18. Palma-Carlos AG, Palma-Carlos ML, Rombaut N. The effect of levocabastine nasal spray in nasal provocation tests. Int J Clin Pharmacol Res 1988; 8 (1): 25-30
19. Corren J, Rachelefsky G, Spector S, et al. Onset and duration of action of levocabastine nasal spray in atopic patients under nasal challenge conditions. J Allergy Clin Immunol 1999; 103 (4): 574-80
20. Schata M, Jorde W, Richarz-Barthauer U. Levocabastine nasal spray better than sodium cromoglycate and placebo in the topical treatment of seasonal allergic rhinitis. J Allergy Clin Immunol 1991; 87 (4): 873-8

21. Hampel FC, Martin BG, Dolen J, et al. Efficacy and safety of levocabastine nasal spray for seasonal allergic rhinitis. Am J Rhinol 1999; 13 (1): 55-62
22. Bende M, Pipkorn U. Topical levocabastine, a selective H1 antagonist, in seasonal allergic rhinoconjunctivitis. Allergy 1987; 42 (7): 512-5
23. Søhoel P, Freng BA, Kramer J, et al. Topical levocabastine compared with orally administered terfenadine for the prophylaxis and treatment of seasonal rhinoconjunctivitis. J Allergy Clin Immunol 1993; 92 (1 Pt 1): 73-81
24. Palma-Carlos AG, Chieira C, Conde TA, et al. Double-blind comparison of levocabastine nasal spray with sodium cromoglycate nasal spray in the treatment of seasonal allergic rhinitis. Ann Allergy 1991; 67 (4): 394-8
25. Knight A. The role of levocabastine in the treatment of allergic rhinoconjunctivitis. Br J Clin Pract 1994; 48 (3): 139-43
26. Kremer B, Tundermann A, Goldschmidt O. Onset of action, effectiveness and tolerance of levocabastine and nedocromil in topical therapy of seasonal allergic rhinoconjunctivitis: The Deutsche Rhinitis-Studiengruppe. Arzneimittel Forschung 1998; 48 (9): 924-30
27. Di Lorenzo G, Gervasi F, Drago A, et al. Comparison of the effects of fluticasone propionate, aqueous nasal spray and levocabastine on inflammatory cells in nasal lavage and clinical activity during the pollen season in seasonal rhinitics. Clin Exp Allergy 1999; 29 (10): 1367-77
28. Ortolani C, Foresi A, Di Lorenzo G, et al. A double-blind, placebo-controlled comparison of treatment with fluticasone propionate and levocabastine in patients with seasonal allergic rhinitis: FLNCO2 Italian Study Group. Allergy 1999; 54 (11): 1173-80
29. Baraldi E, Azzolin NM, Carra S, et al. Effect of topical steroids on nasal nitric oxide production in children with perennial allergic rhinitis: a pilot study. Respir Med 1998; 92 (3): 558-61
30. van de Heyning PH, van Haesendonck J, Creten W, et al. Effect of topical levocabastine on allergic and non-allergic perennial rhinitis: a double-blind study, levocabastine vs placebo, followed by an open, prospective, single-blind study on beclomethasone. Allergy 1988; 43 (5): 386-91
31. International Product Information Document. Livostin Clinical Monograph, Janssen Pharmaceutica, 1995
32. Borum S, Nielsen K, Bisgaard H, et al. Experimentally induced nasal hypersecretion does not reduce the efficacy of intranasal levocabastine. Rhinology 1998; 36 (4): 153-5
33. Dechant KL, Goa KL. Levocabastine: a review of its pharmacological properties and therapeutic potential as a topical antihistamine in allergic rhinitis and conjunctivitis. Drugs 1991; 41 (2): 202-24
34. Heykants J, Van Peer A, Van de Velde V, et al. The pharmacokinetic properties of topical levocabastine: a review. Clin Pharmacokinet 1995; 29 (4): 221-30
35. Okuda M, Tomiyama S, Baba S, et al. Phase I study of R 50547 (levocabastine hydrochloride) nasal spray (1st report): single administration study [in Japanese]. Jibi To Rinsho 1995; 41 Suppl. 1: 281-300
36. Okuda M, Tomiyama S, Ohinishi M, et al. Phase I study of R 50547 (levocabastine hydrochloride) nasal spray (2nd report): repeated administration study [in Japanese]. Jibi To Rinsho 1995; 41 Suppl. 1: 301-25
37. Heykants JJP. Antihistamines. In: Van Boxel CJ, Holford NHG, Danhof M, editors. The in vivo study of drug action. Amsterdam: Elsevier Science, 1992: 337-56
38. Pesco-Koplowitz L, Hassell A, Lee P, et al. Lack of effects of erythromycin and ketoconazole on the pharmacokinetics and pharmacodynamics of steady-state intranasal levocabastine. J Clin Pharmacol 1999; 39 (1): 76-85
39. Frostad AB, Olsen AK. A comparison of topical levocabastine and sodium cromoglycate in the treatment of pollen-provoked allergic conjunctivitis. Clin Exp Allergy 1993; 23 (5): 406-9
40. Davies BH, Mullins J. Topical levocabastine is more effective than sodium cromoglycate for the prophylaxis and treatment of seasonal allergic conjunctivitis. Allergy 1993; 48 (7): 519-24
41. Vermeulen J, Mercer M. Comparison of the efficacy and tolerability of topical levocabastine and sodium cromoglycate in the treatment of seasonal allergic rhinoconjunctivitis in children. Pediatr Allergy Immunol 1994; 5 (4): 209-13
42. Howarth PH. A review of the tolerability and safety of levocabastine eye drops and nasal spray: implications for patient management. Mediators Inflamm 1995; 4 Suppl 1: S26-S30
43. Bahmer FA, Ruprecht KW. Safety and efficacy of topical levocabastine compared with oral terfenadine. Ann Allergy 1994; 72 (5): 429-34
44. A comparison of topical levocabastine and oral terfenadine in the treatment of allergic rhinoconjunctivitis: The Livostin Study Group. Allergy 1993; 48 (7): 530-4
45. Drouin MA, Yang WH, Horak F. Faster onset of action with topical levocabastine than with oral oral cetirizine. Mediators Inflamm 1995; 4 Suppl. 1: S5-S10
46. Azevedo M, Castel-Branco MG, Oliveira JF, et al. Double-blind comparison of levocabastine eye drops with sodium cromoglycate and placebo in the treatment of seasonal allergic conjunctivitis. Clin Exp Allergy 1991; 21 (6): 689-94
47. Wihl JA, Rudblad S, Kjellen H, et al. Levocabastine eye drops versus sodium cromoglycate in seasonal allergic conjunctivitis. Clin Exp Allergy 1991; 21 Suppl. 2: 37-8
48. Busse W, Janssens M, Eisen G, et al. Is there a place for topical antihistamine/decongestant combination in the treatment of seasonal allergic rhinitis? Belgium: Janssen Pharmaceutica, 1995 (Data on file)
49. Kurzawa R, Kossek M, Doniec Z, et al. Clinical efficacy and safety of levocabastine in the therapy in children suffering from seasonal allergic rhinitis and conjunctivitis who are less than 12 year of age. Pol Merkuriusz Lek 1998; 4 (23): 269-72
50. Hermens WA, Merkus FW. The influence of drugs on nasal ciliary movement. Pharm Res 1987; 4 (6): 445-9
51. Merkus FW, Schusler-van Hees MT. Influence of levocabastine suspension on ciliary beat frequency and mucociliary clearance. Allergy 1992; 47 (3): 230-3
52. Rombaut N, Bhatti JZ, Curran S, et al. Effects of topical administration of levocabastine on psychomotor and cognitive function. Ann Allergy 1991; 67 (1): 75-9
53. Arriaga F, Rombaut N. Absence of central effects with levocabastine eye drops. Allergy 1990; 45 (7):552-4
54. Mazzotta P, Loebstein R, Koren G. Treating allergic rhinitis in pregnancy: safety considerations. Drug Saf 1999; 20 (4): 361-75
55. Horak F, Stubner UP. Comparative tolerability of second generation antihistamines. Drug Saf 1999; 20 (5): 385-401
56. McNeely W, Wiseman LR. Intranasal azelastine: a review of its efficacy in the management of allergic rhinitis. Drugs 1998; 56 (1): 91-114
57. Simons FE, Simons KJ. Second-generation H1-receptor antagonists. Ann Allergy 1991; 66 (1): 5-16

58. McTavish D, Sorkin EM. Azelastine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential. Drugs 1989; 38 (5): 778-800
59. ASTA Medica AG. Azelastine product monograph. Frankfurt am Main Germany, 1997 May
60. Ciprandi G, Pronzato C, Passalacqua G, et al. Topical azelastine reduces eosinophil activation and intercellular adhesion molecule-1 expression on nasal epithelial cells: an antiallergic activity. J Allergy Clin Immunol 1996; 98 (6 Pt 1): 1088-96
61. Ciprandi G, Ricca V, Passalacqua G, et al. Seasonal rhinitis and azelastine: long- or short-term treatment? J Allergy Clin Immunol 1997; 99 (3): 301-7
62. Pelucchi A, Chiapparino A, Mastropasqua B, et al. Effect of intranasal azelastine and beclomethasone dipropionate on nasal symptoms, nasal cytology, and bronchial responsiveness to methacholine in allergic rhinitis in response to grass pollens. J Allergy Clin Immunol 1995; 95 (2): 515-23
63. Weiler JM, Meltzer EO, Benson PM, et al. A dose-ranging study of the efficacy and safety of azelastine nasal spray in the treatment of seasonal allergic rhinitis with an acute model. J Allergy Clin Immunol 1994; 94 (6 Pt 1): 972-80
64. Ratner PH, Findlay SR, Hampel F, et al. A double-blind, controlled trial to assess the safety and efficacy of azelastine nasal spray in seasonal allergic rhinitis. J Allergy Clin Immunol 1994; 94 (5): 818-25
65. Meltzer EO, Weiler JM, Dockhorn RJ, et al. Azelastine nasal spray in the management of seasonal allergic rhinitis. Ann Allergy 1994; 72 (4): 354-9
66. LaForce C, Dockhorn RJ, Prenner BM, et al. Safety and efficacy of azelastine nasal spray (Astelin NS) for seasonal allergic rhinitis: a 4-week comparative multicenter trial. Ann Allergy Asthma Immunol 1996; 76 (2): 181-8
67. Herman D, Garay R, Le Gal M. A randomized double-blind placebo controlled study of azelastine nasal spray in children with perennial rhinitis. Int J Pediatr Otorhinolaryngol 1997; 39 (1): 1-8
68. Banov CH, Lieberman P. Efficacy of azelastine nasal spray in the treatment of vasomotor (perennial nonallergic) rhinitis. Ann Allergy Asthma Immunol 2001; 86 (1): 28-35
69. Gehanno P, Deschamps E, Garay E, et al. Vasomotor rhinitis: clinical efficacy of azelastine nasal spray in comparison with placebo. J Otorhinolaryngol Relat Spec 2001; 63 (2): 76-81
70. Berger WE, Fineman SM, Lieberman P, et al. Double-blind trials of azelastine nasal spray monotherapy versus combination therapy with loratadine tablets and beclomethasone nasal spray in patients with seasonal allergic rhinitis: Rhinitis Study Groups. Ann Allergy Asthma Immunol 1999; 82 (6): 535-41
71. Newson-Smith G, Powell M, Baehre M, et al. A placebo controlled study comparing the efficacy of intranasal azelastine and beclomethasone in the treatment of seasonal allergic rhinitis. Eur Arch Otorhinolaryngol 1997; 254 (5): 236-41
72. Davies RJ, Lund VJ, Harten-Ash VJ. The effect of intranasal azelastine and beclomethasone on the symptoms and signs of nasal allergy in patients with perennial allergic rhinitis. Rhinology 1993; 31 (4): 159-64
73. Gastpar H, Aurich R, Petzold U, et al. Intranasal treatment of perennial allergic rhinitis: comparison of azelastine nasal spray and budesonide nasal aerosol. Arzneimittel Forschung 1993; 43 (4): 475-9
74. Dorow P, Aurich R, Petzold U. Efficacy and tolerability of azelastine nasal spray in patients with allergic rhinitis compared to placebo and budesonide. Arzneimittel Forschung 1993; 43 (8): 909-12
75. Stern MA, Wade AG, Ridout SM, et al. Nasal budesonide offers superior symptom relief in perennial allergic rhinitis in comparison to nasal azelastine. Ann Allergy Asthma Immunol 1998; 81 (4): 354-8
76. Mösges R, Spaeth J, Klimek L. Efficacy and tolerability of levocabastine and azelastine nasal sprays for the treatment of allergic rhinitis. Mediators Inflamm 1995; 4 Suppl. 1: S11-5
77. Passali D, Piragine F. A comparison of azelastine nasal spray and cetirizine tablets in the treatment of allergic rhinitis. J Int Med Res 1994; 22 (1): 17-23
78. Charpin D, Godard P, Garay RP, et al. A multicenter clinical study of the efficacy and tolerability of azelastine nasal spray in the treatment of seasonal allergic rhinitis: a comparison with oral cetirizine. Eur Arch Otorhinolaryngol 1995; 252 (8): 455-8
79. Conde Hernández DJ, Palma Aqilar JL, Delgado Romero J. Comparison of azelastine nasal spray and oral ebastine in treating seasonal allergic rhinitis. Curr Med Res Opin 1995; 13 (6): 299-304
80. Gambardella R. A comparison of the efficacy of azelastine nasal spray and loratadine tablets in the treatment of seasonal allergic rhinitis. J Int Med Res 1993; 21 (5): 268-75
81. Gastpar H, Nolte D, Aurich R, et al. Comparative efficacy of azelastine nasal spray and terfenadine in seasonal and perennial rhinitis. Allergy 1994; 49 (3): 152-8
82. British National Formulary. Number 43. Published by the British Medical Association and the Pharmaceutical Society of Great Britain, 2002 Mar
83. Kisicki JC, Howard JR, Riethmuller-Winzen H, et al. Azelastine nasal spray: twenty-nine day tolerability and safety study in healthy subjects. Asta Pharma AG / Carter-Wallace Ltd. CP-90-254; 1990 Jul 2 (Data on file)
84. Weliky I, Howard JR, Wichmann JK. Absolute bioavailability (AB) and pharmacokinetics (PK) of azelastine (AZ) [abstract]. Pharmacol Res 1990; 22 Suppl. 7: S247
85. Riethmuller-Winzen H, Peter G, Buker KM, et al. Tolerability, pharmacokinetics and dose linearity of azelastine hydrochloride in healthy subjects. Arzneimittel Forschung 1994; 44 (10): 1136-40
86. Peter G, Romeis P, Borbe HO, et al. Tolerability and pharmacokinetics of single and multiple doses of azelastine hydrochloride in elderly volunteers. Arzneimittel Forschung 1995; 45 (5): 576-81
87. Kisicki JC, Herman R, Niebch G. Amendment No. 1 to the report: azelastine nasal spray: twenty-nine day tolerability and safety study in healthy subjects. Asta Pharma AG / Carter-Wallace Ltd. CP-90-254; 1993 Apr 23 (Data on file)
88. Wallace Laboratories. Azelastine hydrochloride nasal spray prescribing information. New Jersey, USA, 1997
89. Wober W, Diez Crespo C, Bahre M. Efficacy and tolerability of azelastine nasal spray in the treatment of allergic rhinitis: large scale experience in community practice. Curr Med Res Opin 1997; 13 (10): 617-26
90. MacMahon MT, Newson-Smith G, Granham SP, et al. Intranasal azelastine in seasonal allergic rhinitis [abstract]. Proceedings of the 95th Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics; 1994 Mar 30-Apr 1; New Orleans (LA): 184
91. Boné Calvo J, Botey Sala J, Caballero Goméz L. Long term safety and efficacy of azelastine HCl nasal spray in the treatment of children with perennial allergic rhinitis. Acta Pediatr Esp 1996; 54 (10): 750-64

92. Gastpar H, Dorow P, Aurich R, et al. Investigation of long-term efficacy and tolerability of azelastine nasal spray in the treatment of perennial allergic rhinitis. Arzneimittel Forschung 1993; 43 (7): 771-6
93. Storms WW, Pearlman DS, Chervinsky P, et al. Effectiveness of azelastine nasal solution in seasonal allergic rhinitis. Ear Nose Throat J 1994; 73 (6): 382-6, 390-4
94. Cua-Lim F, Cua PE, Perez A. The efficacy and safety of azelastine nasal spray in perennial allergic rhinitis in Philipinos [abstract]. Allergy 1997; 52 Suppl. 37: 209
95. Weiler JM, Meltzer EO. Azelastine nasal spray as adjunctive therapy to azelastine tablets in the management of seasonal allergic rhinitis. Ann Allergy Asthma Immunol 1997; 79 (4): 327-32
96. Kakiuchi M, Ohashi T, Tanaka K, et al. Central nervous system effects of the novel antiallergic agent HSR-609 and typical antiallergic agents using behavioral and electroencephalographic analyses in dogs. Nihon Shinkei Seishin Yakurigaku Zasshi 1998; 18 (5): 189-99
97. Lassig W, Wober W, Hoflich C, et al. Topical therapy of allergic rhinitis in childhood: allergodil nasal spray-non-sedating in children. Curr Med Res Opin 1996; 13 (7): 391-5
98. Spaeth J, Klimek L, Mosges R. Sedation in allergic rhinitis is caused by the condition and not by antihistamine treatment. Allergy 1996; 51 (12): 893-906
99. Woosley RL, Sale M. QT interval: a measure of drug action. Am J Cardiol 1993; 72 (6): 36B-43B
100. Kane GC, Lipsky JJ. Drug-grapefruit juice interactions. Mayo Clin Proc 2000; 75 (9): 933-42
101. Bronsky EA, Meltzer EO, Perhach JL, et al. Cardiac safety of azelastine following 8 weeks of intra-nasal administration [abstract]. J Allergy Clin Immunol 1997; 99 (Pt 2): S445
102. DuBuske LM. Second-generation antihistamines: the risk of ventricular arrhythmias. Clin Ther 1999; 21 (2): 281-95
103. Mygind N. Local effect of intranasal beclomethasone dipropionate aerosol in hay fever. BMJ 1973; 4 (5890): 464-6
104. Barnes PJ. Molecular mechanisms of glucocorticoid action in asthma. Pulm Pharmacol Ther 1997; 10 (1): 3-19
105. International Consensus Report on the diagnosis and management of rhinitis: International Rhinitis Management Working Group. Allergy 1994; 49 (19 Suppl): 1-34
106. Dykewicz MS, Fineman S, Nicklas R, et al. Joint task force algorithm and annotations for diagnosis and management of rhinitis. Ann Allergy Asthma Immunol 1998; 81 (5 Pt 2): 469-73
107. van Cauwenberge P, Bachert C, Passalacqua G, et al. Consensus statement on the treatment of allergic rhinitis: European Academy of Allergology and Clinical Immunology. Allergy 2000; 55 (2): 116-34
108. Weiner JM, Abramson MJ, Puy RM. Intranasal corticosteroids versus oral H1 receptor antagonists in allergic rhinitis: systematic review of randomised controlled trials. BMJ 1998; 317 (7173): 1624-9
109. Svensson C, Andersson M, Greiff L, et al. Effects of topical budesonide and levocabastine on nasal symptoms and plasma exudation responses in seasonal allergic rhinitis. Allergy 1998; 53 (4): 367-74
110. Bousquet J, Chanal I, Alquie MC, et al. Prevention of pollen rhinitis symptoms: comparison of fluticasone propionate aqueous nasal spray and disodium cromoglycate aqueous nasal spray: a multicenter, double-blind, double-dummy, parallel-group study. Allergy 1993; 48 (5): 327-33
111. Fisher WG. Comparison of budesonide and disodium cromoglycate for the treatment of seasonal allergic rhinitis in children. Ann Allergy 1994; 73 (6): 515-20
112. Nielsen LP, Mygind N, Dahl R. Intranasal corticosteroids for allergic rhinitis: superior relief? Drugs 2001; 61 (11): 1563-79
113. Aubier M, Levy J, Clerici C, et al. Different effects of nasal and bronchial glucocorticosteroid administration on bronchial hyperresponsiveness in patients with allergic rhinitis. Am Rev Respir Dis 1992; 146 (1): 122-6
114. Corren J, Adinoff AD, Buchmeier AD, et al. Nasal beclomethasone prevents the seasonal increase in bronchial responsiveness in patients with allergic rhinitis and asthma. J Allergy Clin Immunol 1992; 90 (2): 250-6
115. Foresi A, Pelucchi A, Gherson G, et al. Once daily intranasal fluticasone propionate (200 micrograms) reduces nasal symptoms and inflammation but also attenuates the increase in bronchial responsiveness during the pollen season in allergic rhinitis. J Allergy Clin Immunol 1996; 98 (2): 274-82
116. Reed CE, Marcoux JP, Welsh PW. Effects of topical nasal treatment on asthma symptoms. J Allergy Clin Immunol 1988; 81 (5 Pt 2): 1042-7
117. Wood RA, Eggleston PA. The effects of intranasal steroids on nasal and pulmonary responses to cat exposure. Am J Respir Crit Care Med 1995; 151 (2 Pt 1): 315-20
118. Henriksen JM, Wenzel A. Effect of an intranasally administered corticosteroid (budesonide) on nasal obstruction, mouth breathing, and asthma. Am Rev Respir Dis 1984; 130 (6): 1014-8
119. Berkowitz RB, Bernstein DI, LaForce C, et al. Onset of action of mometasone furoate nasal spray (NASONEX) in seasonal allergic rhinitis. Allergy 1999; 54 (1): 64-9
120. Selner JC, Weber RW, Richmond GW, et al. Onset of action of aqueous beclomethasone dipropionate nasal spray in seasonal allergic rhinitis. Clin Ther 1995; 17 (6): 1099-109
121. Holm AF, Fokkens WJ, Godthelp T, et al. A 1-year placebo-controlled study of intranasal fluticasone propionate aqueous nasal spray in patients with perennial allergic rhinitis: a safety and biopsy study. Clin Otolaryngol 1998; 23 (1): 69-73
122. Juniper EF, Guyatt GH, O'Byrne PM, et al. Aqueous beclomethasone diproprionate nasal spray: regular versus "as required" use in the treatment of seasonal allergic rhinitis. J Allergy Clin Immunol 1990; 86 (3 Pt 1): 380-6
123. Banov CH, Woehler TR, LaForce CF, et al. Once daily intranasal fluticasone propionate is effective for perennial allergic rhinitis. Ann Allergy 1994; 73 (3): 240-6
124. Bhatia M, Campbell LM, Ross JR, et al. Intranasal budesonide once daily in seasonal allergic rhinitis. Curr Med Res Opin 1991; 12 (5): 287-95
125. Drouin M, Yang WH, Bertrand B, et al. Once daily mometasone furoate aqueous nasal spray is as effective as twice daily beclomethasone dipropionate for treating perennial allergic rhinitis patients. Ann Allergy Asthma Immunol 1996; 77 (2): 153-60
126. Howarth PH. A comparison of the anti-inflammatory properties of intranasal corticosteroids and antihistamines in allergic rhinitis. Allergy 2000; 55 Suppl. 62: 6-11
127. Esmailpour N, Hogger P, Rohdewald P. Binding of glucocorticoids to human nasal tissue in vitro. Int Arch Allergy Immunol 2000; 122 (2): 151-4
128. Petersen H, Kullberg A, Edsbacker S, et al. Nasal retention of budesonide and fluticasone in man: formation of airway mucosal budesonide-esters in vivo. Br J Clin Pharmacol 2001; 51 (2): 159-63

129. Newman SP, Moren PF, Clarke SW. The nasal distribution of metered dose inhalers. J Laryngol Otol 1987; 101 (2): 127-32
130. Newman SP, Moren F, Clarke SW. Deposition pattern of nasal sprays in man. Rhinology 1988; 26 (2): 111-20
131. Thorsson L, Newman SP, Weisz A, et al. Nasal distribution of budesonide inhaled via a powder inhaler. Rhinology 1993; 31 (1): 7-10
132. Thorsson L, Borga O, Edsbacker S. Systemic availability of budesonide after nasal administration of three different formulations: pressurized aerosol, aqueous pump spray, and powder. Br J Clin Pharmacol 1999; 47 (6): 619-24
133. Daley-Yates PT, Baker RC. Systemic bioavailability of fluticasone propionate administered as nasal drops and aqueous nasal spray formulations. Br J Clin Pharmacol 2001; 51 (1): 103-5
134. Hardy JG, Lee SW, Wilson CG. Intranasal drug delivery by spray and drops. J Pharm Pharmacol 1985; 37 (5): 294-7
135. Bryant ML, Brown P, Gurevich N, et al. Comparison of the clearance of radiolabelled nose drops and nasal spray as mucosally delivered vaccine. Nucl Med Commun 1999; 20 (2): 171-4
136. Argenti D, Colligon I, Heald D, et al. Nasal mucosal inflammation has no effect on the absorption of intranasal triamcinolone acetonide. J Clin Pharmacol 1994; 34 (8): 854-8
137. Greiff L, Andersson M, Svensson J, et al. Absorption across the nasal airway mucosa in house dust mite perennial allergic rhinitis. Clin Physiol Funct Imaging 2002; 22 (1): 55-7
138. Lipworth BJ, Jackson CM. Safety of inhaled and intranasal corticosteroids: lessons for the new millennium. Drug Saf 2000; 23 (1): 11-33
139. Lee DK, Robb FM, Sims EJ, et al. Systemic bioactivity of intranasal triamcinolone and mometasone in perennial allergic rhinitis. Br J Clin Pharmacol 2003; 55 (3): 310-3
140. Wilson AM, Sims EJ, McFarlane LC, et al. Effects of intranasal corticosteroids on adrenal, bone, and blood markers of systemic activity in allergic rhinitis. J Allergy Clin Immunol 1998; 102 (4 Pt 1): 598-604
141. Toft A, Wihl JA, Toxman J, et al. Double-blind comparison between beclomethasone dipropionate as aerosol and as powder in patients with nasal polyposis. Clin Allergy 1982; 12 (4): 391-401
142. LaForce C. Use of nasal steroids in managing allergic rhinitis. J Allergy Clin Immunol 1999; 103 (3 Pt 2): S388-94
143. Graft D, Aaronson D, Chervinsky P, et al. A placebo- and active-controlled randomized trial of prophylactic treatment of seasonal allergic rhinitis with mometasone furoate aqueous nasal spray. J Allergy Clin Immunol 1996; 98 (4): 724-31
144. Andersson M, Berglund R, Greiff L, et al. A comparison of budesonide nasal dry powder with fluticasone propionate aqueous nasal spray in patients with perennial allergic rhinitis. Rhinology 1995; 33 (1): 18-21
145. Soderberg-Warner ML. Nasal septal perforation associated with topical corticosteroid therapy. J Pediatr 1984; 105 (5): 840-1
146. Cervin A, Andersson M. Intranasal steroids and septum perforation – an overlooked complication? A description of the course of events and a discussion of the causes. Rhinology 1998; 36 (3): 128-32
147. Bircher AJ, Pelloni F, Langauer-Messmer S, et al. Delayed hypersensitivity reactions to corticosteroids applied to mucous membranes. Br J Dermatol 1996; 135 (2): 310-3
148. Gonzalo-Garijo MA, Bobadilla-Gonzalez P. Cutaneous-mucosal allergic contact reaction due to topical corticosteroids. Allergy 1995; 50 (10): 833-6
149. Lipworth BJ, Seckl JR. Measures for detecting systemic bioactivity with inhaled and intranasal corticosteroids. Thorax 1997; 52 (5): 476-82
150. Crowley S, Hindmarsh PC, Holownia P, et al. The use of low doses of ACTH in the investigation of adrenal function in man. J Endocrinol 1991; 130 (3): 475-9
151. Homer JJ, Gazis TG. Cushing's syndrome induced by betamethasone nose drops: in rhinological disease betamethasone should be regarded as systemic corticosteroid [letter]. BMJ 1999; 318 (7194): 1355
152. Malozowski S, Purucker M, Worobec A. Cushing's syndrome induced by betamethasone nose drops: children taking intranasal corticosteroids should be monitored for growth retardation [letter]. BMJ 1999; 318 (7194): 1355
153. Findlay CA, Macdonald JF, Wallace AM, et al. Childhood Cushing's syndrome induced by betamethasone nose drops, and repeat prescriptions. BMJ 1998; 317 (7160): 739-40
154. Stevens DJ. Cushing's syndrome due to the abuse of betamethasone nasal drops. J Laryngol Otol 1988; 102 (3): 219-21
155. Nutting CM, Page SR. Iatrogenic Cushing's syndrome due to nasal betamethasone: a problem not to be sniffed at! Postgrad Med J 1995; 71 (834): 231-2
156. Passalacqua G, Albano M, Canonica GW, et al. Inhaled and nasal corticosteroids: safety aspects. Allergy 2000; 55 (1): 16-33
157. Cave A, Arlett P, Lee E. Inhaled and nasal corticosteroids: factors affecting the risks of systemic adverse effects. Pharmacol Ther 1999; 83 (3): 153-79
158. Wilson AM, McFarlane LC, Lipworth BJ. Effects of repeated once daily dosing of three intranasal corticosteroids on basal and dynamic measures of hypothalamic-pituitary-adrenal-axis activity. J Allergy Clin Immunol 1998; 101 (4 Pt 1): 470-4
159. Knutsson U, Stierna P, Marcus C, et al. Effects of intranasal glucocorticoids on endogenous glucocorticoid peripheral and central function. J Endocrinol 1995; 144 (2): 301-10
160. Davies RJ, Nelson HS. Once-daily mometasone furoate nasal spray: efficacy and safety of a new intranasal glucocorticoid for allergic rhinitis. Clin Ther 1997; 19 (1): 27-38
161. Nayak AS, Ellis MH, Gross GN, et al. The effects of triamcinolone acetonide aqueous nasal spray on adrenocortical function in children with allergic rhinitis. J Allergy Clin Immunol 1998; 101 (2 Pt 1): 157-62
162. Howland WC, Dockhorn R, Gillman S, et al. A comparison of effects of triamcinolone acetonide aqueous nasal spray, oral prednisone, and placebo on adrenocortical function in male patients with allergic rhinitis. J Allergy Clin Immunol 1996; 98 (1): 32-8
163. Munk ZM, LaForce C, Furst JA, et al. Efficacy and safety of triamcinolone acetonide aqueous nasal spray in patients with seasonal allergic rhinitis. Ann Allergy Asthma Immunol 1996; 77 (4): 277-81
164. Vargas R, Dockhorn RJ, Findlay SR, et al. Effect of fluticasone propionate aqueous nasal spray versus oral prednisone on the hypothalamic-pituitary-adrenal axis. J Allergy Clin Immunol 1998; 102 (2): 191-7
165. Storms WW. Risk-benefit assessment of fluticasone propionate in the treatment of asthma and allergic rhinitis. J Asthma 1998; 35 (4): 313-36
166. Brannan MD, Herron JM, Reidenberg P, et al. Lack of hypothalamic-pituitary-adrenal axis suppression with once-daily or twice-daily beclomethasone dipropionate aqueous nasal spray

administered to patients with allergic rhinitis. Clin Ther 1995; 17 (4): 637-47
167. Lumry WR. A review of the preclinical and clinical data of newer intranasal steroids used in the treatment of allergic rhinitis. J Allergy Clin Immunol 1999; 104 (4 Pt 1): S150-8
168. Onrust SV, Lamb HM. Mometasone furoate: a review of its intranasal use in allergic rhinitis. Drugs 1998; 56 (4): 725-45
169. Grossman J, Banov C, Bronsky EA, et al. Fluticasone propionate aqueous nasal spray is safe and effective for children with seasonal allergic rhinitis. Pediatrics 1993; 92 (4): 594-9
170. Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy: a systematic review and meta-analysis. Arch Intern Med 1999; 159 (9): 941-55
171. Fokkens WJ, van de Merwe JP, Braat JP, et al. The effect of intranasal and inhaled corticosteroids in healthy volunteers on the number of circulating lymphocytes and lymphocyte subsets. Allergy 1999; 54 (2): 158-64
172. Wilson AM, Lipworth BJ. 24-Hour and fractionated profiles of adrenocortical activity in asthmatic patients receiving inhaled and intranasal corticosteroids. Thorax 1999; 54 (1): 20-6
173. Daley-Yates PT. Pharmacokinetic (PK) and pharmacodynamic (PD) data for inhaled and intranasal corticosteroids (CS) reassessed using a physiological PK/PD model [abstract]. Eur Respir J 2001; 18 Suppl. 33: 147S
174. Skoner DP, Rachelefsky GS, Meltzer EO, et al. Detection of growth suppression in children during treatment with intranasal beclomethasone dipropionate [abstract]. Pediatrics 2000; 105 (2): E23
175. Wolthers OD, Pedersen S. Knemometric assessment of systemic activity of once daily intranasal dry-powder budesonide in children. Allergy 1994; 49 (2): 96-9
176. Richards DH, Daley-Yates PT. Choice of inhaled and intranasal steroids when used in combination for asthma and rhinitis in children [abstract]. Allergy 2000; 55 Suppl. 63: A185
177. Agertoft L, Pedersen S. Short-term lower leg growth rate in children with rhinitis treated with intranasal mometasone furoate and budesonide. J Allergy Clin Immunol 1999; 104 (5): 948-52
178. Schenkel EJ, Skoner DP, Bronsky EA, et al. Absence of growth retardation in children with perennial allergic rhinitis after one year of treatment with mometasone furoate aqueous nasal spray [abstract]. Pediatrics 2000; 105 (2): E22
179. Scadding GK, Richards DH. Steroid selection can reduce potential for steroid load [electronic letter]. British Medical Journal [online]. Available from URL: http//bmj.com/cgi/eletters/324/7350/1374 [Accessed 2002 Jul 27]
180. Kallen B, Rydhstroem H, Aberg A. Congenital malformations after the use of inhaled budesonide in early pregnancy. Obstet Gynecol 1999; 93 (3): 392-5
181. Edelman DA, van Os WAA. Safety of intranasal beclomethasone dipropionate: a review. Respir Care 1996, 30
182. Edwards TB. Effectiveness and safety of beclomethasone dipropionate, an intranasal corticosteroid, in the treatment of patients with allergic rhinitis. Clin Ther 1995; 17 (6): 1032-41
183. Daley-Yates PT, Price AC, Sisson JR, et al. Beclomethasone dipropionate: absolute bioavailability, pharmacokinetics and metabolism following intravenous, oral, intranasal and inhaled administration in man. Br J Clin Pharmacol 2001; 51 (5): 400-9
184. Wihl JA, Andersson KE, Johansson SA. Systemic effects of two nasally administered glucocorticosteroids. Allergy 1997; 52 (6): 620-6
185. Rachelefsky GS, Chervinsky P, Meltzer EO, et al. An evaluation of the effects of beclomethasone dipropionate aqueous nasal spray [Vancenase AQ (VNS)] on long-term growth in children [abstract]. J Allergy Clin Immunol 1998; 101: 978A
186. Fraunfelder FT, Meyer SM. Posterior subcapsular cataracts associated with nasal or inhalation corticosteroids. Am J Ophthalmol 1990; 109 (4): 489-90
187. Derby L, Maier WC. Risk of cataract among users of intranasal corticosteroids. J Allergy Clin Immunol 2000; 105 (5): 912-6
188. Garbe E, LeLorier J, Boivin JF, et al. Inhaled and nasal glucocorticoids and the risks of ocular hypertension or open-angle glaucoma. JAMA 1997; 277 (9): 722-7
189. GDS/96/044, GlaxoSmithKline, 1996 (Data on file)
190. Mygind N. Effects of beclomethasone dipropionate aerosol on nasal mucosa. Br J Clin Pharmacol 1977; 4 Suppl. 3: 287S-91S
191. Mygind N, Sorensen H, Pedersen CB. The nasal mucosa during long-term treatment with beclomethasone dipropionate aerosol: a light-and scanning electron microscopic study of nasal polyps. Acta Otolaryngol 1978; 85 (5-6): 437-43
192. WPSP/01/032, GlaxoSmithKline, 2001 (Data on file)
193. Beconase Patient Information Leaflet, GlaxoSmithKline
194. GSK Key Opinion Leader Development Programme, GlaxoSmithKline, 2002 (Data on file)
195. Synnerstad B, Lindqvist N. A clinical comparison of intranasal budesonide with beclomethasone dipropionate for perennial non-allergic rhinitis: a 12 month study. Br J Clin Pract 1996; 50 (7): 363-6
196. Lindqvist N, Balle VH, Karma P, et al. Long-term safety and efficacy of budesonide nasal aerosol in perennial rhinitis: a 12-month multicentre study. Allergy 1986; 41 (3): 179-86
197. Pipkorn U, Pukander J, Suonpaa J, et al. Long-term safety of budesonide nasal aerosol: a 5.5-year follow-up study. Clin Allergy 1988; 18 (3): 253-9
198. Wolthers OD, Pedersen S. Short-term growth in children with allergic rhinitis treated with oral antihistamine, depot and intranasal glucocorticosteroids. Acta Paediatr 1993; 82 (8): 635-40
199. Dent G. Ciclesonide (Byk Gulden). Curr Opin Investig Drugs 2002; 3 (1): 78-83
200. Schmidt BM, Timmer W, Georgens AC, et al. The new topical steroid ciclesonide is effective in the treatment of allergic rhinitis. J Clin Pharmacol 1999; 39 (10): 1062-9
201. Weinbrenner A, Huneke D, Zschiesche M, et al. Circadian rhythm of serum cortisol after repeated inhalation of the new topical steroid ciclesonide. J Clin Endocrinol Metab 2002; 87 (5): 2160-3
202. Physicians Desk Reference. 52nd ed. Medical Economics Company; 1998. Nasarel (flunisolide) Nasal Solution, 0.025%. Montvale (NJ). 889-91
203. Gillman SA, Anolik R, Schenkel E, et al. One-year trial on safety and normal linear growth with flunisolide HFA in children with asthma. Clin Pediatr (Phila) 2002; 41 (5): 333-40
204. Harding SM. The human pharmacology of fluticasone propionate. Respir Med 1990; 84 Suppl. A: 25-9
205. van As A, Bronsky E, Grossman J, et al. Dose tolerance study of fluticasone propionate aqueous nasal spray in patients with seasonal allergic rhinitis. Ann Allergy 1991; 67 (2 Pt 1): 156-62
206. Bronsky EA, Dockhorn RJ, Meltzer EO, et al. Fluticasone propionate aqueous nasal spray compared with terfenadine tablets in the treatment of seasonal allergic rhinitis. J Allergy Clin Immunol 1996; 97 (4): 915-21

207. Gulant SP, Ahrens RC, Dockhorn RJ, et al. Treatment of seasonal allergic rhinitis with once-daily intranasal fluticasone propionate therapy in children: Fluticasone Propionate Collaborative Pediatric Working Group. J Pediatr 1994; 125 (4): 628-34
208. Howland WC. Fluticasone propionate: topical or systemic effects? Clin Exp Allergy 1996; 26 Suppl. 3: 18-22
209. BL2001/00003/00, GlaxoSmithKline, 2001 (Data on file)
210. Konig P, Ford L, Galant S, et al. A 1-year comparison of the effects of inhaled fluticasone propionate (FP) and placebo on growth in prepubescent children with asthma [abstract]. Eur Respir J 1996; 9 (294s): 1860
211. Bond DW, Charlton CP, Gregson RM. Drug points: benign intracranial hypertension secondary to nasal fluticasone propionate. BMJ 2001; 322 (7291): 897
212. Chen CC, Baroody FM, Reed KD, et al. Effects of one year treatment with fluticasone propionate aqueous nasal spray (FPANS) and terfenadine (TER) on the nasal mucosa: a safety study using electron and light microscopy [abstract no. S497]. J Allergy Clin Immunol 1997; 99 (1 Pt 2): 2013
213. Braat JP, Ainge G, Bowles JA, et al. The lack of effect of benzalkonium chloride on the cilia of the nasal mucosa in patients with perennial allergic rhinitis: a combined functional, light, scanning and transmission electron microscopy study. Clin Exp Allergy 1995; 25 (10): 957-65
214. Scadding GK, Lund VJ, Holmstrom M, et al. Clinical and physiological effects of fluticasone propionate aqueous nasal spray in the treatment of perennial rhinitis. Rhinol Suppl 1991; 11: 37-43
215. BL2001/00003/00, GlaxoSmithKline, 2001 (Data on file)
216. Flixonase Summary of Product Characteristics, GlaxoSmithKline
217. Flixonase Medical Workshop Proceedings, London: Synergy Medical Education, 2002 Dec
218. GlaxoSmithKline Clinical Expert Report for Flixonase, GlaxoSmithKline, 2001
219. GlaxoSmithKline Safety Reports WSP/99/010 and WPSP/99/037, GlaxoSmithKline, 1999
220. Brannan MD, Seiberling M, Cutler DL, et al. Lack of systemic activity with intranasal mometasone furoate. J Allergy Clin Immunol 1996; 97 (1 Pt 3): 198
221. Brannan MD, Herron JM, Affrime MB. Safety and tolerability of once-daily mometasone furoate aqueous nasal spray in children [abstract]. Clin Ther 1997; 19 (6): 1330-9
222. Meltzer EO, Berger WE, Berkowitz RB, et al. A dose-ranging study of mometasone furoate aqueous nasal spray in children with seasonal allergic rhinitis. J Allergy Clin Immunol 1999; 104 (1): 107-14
223. Dibildox J. Safety and efficacy of mometasone furoate aqueous nasal spray in children with allergic rhinitis: results of recent clinical trials. J Allergy Clin Immunol 2001; 108 (1 Suppl.): S54-8
224. Minshall E, Ghaffar O, Cameron L, et al. Assessment by nasal biopsy of long-term use of mometasone furoate aqueous nasal spray (Nasonex) in the treatment of perennial rhinitis. Otolaryngol Head Neck Surg 1998; 118 (5): 648-54
225. Meltzer EO, Jalowayski AA, Orgel HA, et al. Subjective and objective assessments in patients with seasonal allergic rhinitis: effects of therapy with mometasone furoate nasal spray. J Allergy Clin Immunol 1998; 102 (1): 39-49
226. Welch MJ, Bronsky E, Findlay S, et al. Long-term safety of triamcinolone acetonide nasal aerosol for the treatment of perennial allergic rhinitis. Clin Ther 1994; 16 (2): 253-62
227. Koepke JW, Beaucher WN, Kobayashi RH, et al. Long-term safety and efficacy of triamcinolone acetonide aqueous nasal spray for the treatment of perennial allergic rhinitis. Allergy Asthma Proc 1997; 18 (1): 33-7
228. Feiss G, Morris R, Rom D, et al. A comparative study of the effects of intranasal triamcinolone acetonide aerosol (ITAA) and prednisone on adrenocortical function. J Allergy Clin Immunol 1992; 89 (6): 1151-6
229. Tinkelman D, Falliers C, Gross G, et al. Multicenter evaluation of triamcinolone acetonide nasal aerosol in the treatment of adult patients with seasonal allergic rhinitis. Ann Allergy 1990; 64 (2 Pt 2): 234-40
230. Spector S, Bronsky E, Chervinsky P, et al. Multicenter, double-blind, placebo-controlled trial of triamcinolone acetonide nasal aerosol in the treatment of perennial allergic rhinitis. Ann Allergy 1990; 64 (3): 300-5
231. Settipane G, Korenblat PE, Winder J, et al. Triamcinolone acetonide aqueous nasal spray in patients with seasonal ragweed allergic rhinitis: a placebo-controlled, double-blind study. Clin Ther 1995; 17 (2): 252-63
232. Storms W, Bronsky E, Findlay S, et al. Once daily triamcinolone acetonide nasal spray is effective for the treatment of perennial allergic rhinitis. Ann Allergy 1991; 66 (4): 329-34
233. Laliberte F, Laliberte MF, Lecart S, et al. Clinical and pathologic methods to assess the long-term safety of nasal corticosteroids: French Triamcinolone Acetonide Study Group. Allergy 2000; 55 (8): 718-22
234. Klossek JM, Laliberte F, Laliberte MF, et al. Local safety of intranasal triamcinolone acetonide: clinical and histological aspects of nasal mucosa in the long-term treatment of perennial allergic rhinitis. Rhinology 2001; 39 (1): 17-22
235. Passali D, Mosges R, Hassan H, et al. International Conference on Allergic Rhinitis in Childhood. Allergy 1999; 54 Suppl. 55: 4-34
236. Warner JO. Early treatment of the atopic child. Pediatr Allergy Immunol 1997; 8 (10 Suppl.): 46-8
237. Iikura Y, Naspitz CK, Mikawa H, et al. Prevention of asthma by ketotifen in infants with atopic dermatitis. Ann Allergy 1992; 68 (3): 233-6
238. Vuurman EF, van Veggel LM, Uiterwijk MM, et al. Seasonal allergic rhinitis and antihistamine effects on children's learning. Ann Allergy 1993; 71 (2): 121-6
239. Ellegard E, Karlsson G. Nasal congestion during the menstrual cycle. Clin Otolaryngol 1994; 19 (5): 400-3
240. Ellegard E, Karlsson G. Nasal congestion during pregnancy. Clin Otolaryngol 1999; 24 (4): 307-11
241. Ellegard E, Karlsson G. IgE-mediated reactions and hyperreactivity in pregnancy rhinitis. Arch Otolaryngol Head Neck Surg 1999; 125 (10): 1121-5
242. Greenberger PA, Patterson R. Beclomethasone diproprionate for severe asthma during pregnancy. Ann Intern Med 1983; 98 (4): 478-80
243. Saxen I. Cleft palate and maternal diphenhydramine intake [letter]. Lancet 1974; I (7854): 407-8
244. Saxen I. Associations between oral clefts and drugs taken during pregnancy. Int J Epidemiol 1975; 4 (1): 37-44
245. Einarson A, Bailey B, Jung G, et al. Prospective controlled study of hydroxyzine and cetirizine in pregnancy. Ann Allergy Asthma Immunol 1997; 78 (2): 183-6
246. Yanez A, Rodrigo GJ. Intranasal corticosteroids versus topical H1 receptor antagonists for the treatment of allergic rhinitis: a systematic review with meta-analysis. Ann Allergy Asthma Immunol 2002; 89 (5): 479-84

247. Foresi A. A comparison of the clinical efficacy and safety of intranasal fluticasone propionate and antihistamines in the treatment of rhinitis. Allergy 2000; 55 Suppl. 62: 12-4
248. Allen DB. Do intranasal corticosteroids affect childhood growth? Allergy 2000; 55 Suppl. 62: 15-8
249. van Bavel J, Findlay SR, Hampel FC, et al. Intranasal fluticasone propionate is more effective than terfenadine tablets for seasonal allergic rhinitis. Arch Intern Med 1994; 154 (23): 2699-704
250. Trangsrud AJ, Whitaker AL, Small RE. Intranasal corticosteroids for allergic rhinitis. Pharmacotherapy 2002; 22 (11): 1458-67
251. Kaszuba SM, Baroody FM, deTineo M, et al. Superiority of an intranasal corticosteroid compared with an oral antihistamine in the as-needed treatment of seasonal allergic rhinitis. Arch Intern Med 2001; 161 (21): 2581-7

Correspondence and offprints: Dr *Rami Jean Salib*, Respiratory Cell and Molecular Biology Sub-Division, Infection, Inflammation and Repair, Centre Block (MP 810), Southampton General Hospital, Tremona Road, Southampton, SO16 6YD, UK.
E-mail: rjs4@soton.ac.uk