Allergy 2003: 58: 192–197
Printed in UK. All rights reserved

ALLERGY
ISSN 0105-4538

News and commentaries

Requirements for medications commonly used in the treatment of allergic rhinitis

European Academy of Allergy and Clinical Immunology (EAACI) Allergic Rhinitis and its Impact on Asthma (ARIA)

Chairs: Jean Bousquet, Paul Van Cauwenberge; Members: Claus Bachert, Giorgio W Canonica, Pascal Demoly, Stephen R Durham, Wystske Fokkens, Richard Lockey, Eli O Meltzer, Joaquim Mullol, Robert M Naclerio, David Price, F Estelle R Simons, Antonio M Vignola, John O Warner

Introduction:

It has been shown that several medications are effective in the treatment of allergic rhinitis (1–3). Among them, oral H1-antihistamines and intra-nasal corticosteroids are the most widely used.

A large number of studies have been carried out with these drugs but they use various end points which make these studies difficult to be compared. Moreover, the pharmacological properties of these drugs are well known but recently, new data have focussed on the mechanisms of action of H1-antihistamines and their so-called "anti-allergic" properties.

Guidelines for the development of drugs used in allergic rhinitis are pending. It seemed therefore important before proposing recommendations for such guidelines to define the properties of oral H1-antihistamines, anti-allergic effects of H1-antihistamines and intra-nasal corticosteroids.

There is therefore an urgent need to make internationally valid definitions. These will be of importance for physicians and scientists but also for drug companies developing new drugs and registration authorities.

1-Oral H1-antihistamines:

Definition:

H1-blockers or H1-antihistamines are drugs with blocking activity at the H1 histamine receptor level. Some also possess additional anti-allergic properties. During the last 20 years, pharmacological research has produced compounds with higher potency, longer duration of action, faster onset of action and minimal sedative effect and impairment: the so-called second generation H1-antihistamines, as opposed to the first generation H1-antihistamines (3). The term "third" generation should be reserved for a H1-antihistamine with novel properties, not necessarily anti-allergic.

Pharmacological properties:

Although a number of mediators are involved in the pathophysiology of allergic symptoms, histamine remains a major one. Histamine acts, in the nose, predominantly via H1 receptors (4). The role of H2 and H3 receptors has not been fully clarified. Unlike histamine, binding of the antagonists to the receptors does not elicit a tissue response. Inverse agonism, i.e., stabilisation of an inactive conformation of the histamine H1 receptor, may be a key component of the mechanism of action of H1-antihistamines and it has been proposed by some to rename this class of drugs as "inverse H1-receptor agonists" (5). However, these effects have not been demonstrated *in vivo*.

Over the past 20 years, it has become clear that many H1-antihistamines have "anti-allergic properties" in addition to their H1-receptor blockage properties (6). These vary depending on the molecule and target organ (see below) (7).

Pharmacokinetics:

Most of the new oral H1-antihistamines have a fast onset of action (20 minutes to 2 hours) and a duration of effect that last up to 24 hours. Acrivastine has a shorter duration of action and should be administered twice daily. Intra-nasal H1-antihistamines have a faster onset of action but these medications also need to be administered twice daily (for review see (3)).

Certain foods have been found to alter the absorption of some oral H1-antihistamines. The absorption of many drugs can also be affected by their interaction with ATP-binding cassette (ABC) transporters. The most extensively studied of these ABC transporters is the protein product of MDR1 (multidrug resistance) that encodes a 170-kDa integral plasma membrane phosphorylated glycoprotein known as P-glycoprotein (P-gp). Grapefruit, orange, and apple juices decrease the oral availability of

some oral H1-antihistamines by interacting with P-gp (8) and organic anion transport polypeptide (OATP) (9).

Some oral H1-antihistamines undergo hepatic metabolism via the cytochrome P450 system and are transformed into active metabolites. Cytochrome P4503A (CYP3A) is importantly involved in the metabolism of many chemically diverse drugs administered to humans and can lead to drug-drug interactions (10).

Efficacy:

H1-histamine stimulation of the nasal mucosa produces the classical symptoms of allergic rhinitis e.g. sneezing, itching, rhinorrhea and congestion both in adults and children (11). These symptoms can therefore be controlled by administering H1-antihistamines.

However, oral H1-antihistamines are usually less effective against nasal obstruction because other mediators, and histamine acting through the H3 receptor, impact this symptom. Some studies have found that some drugs significantly reduce nasal congestion, although the magnitude of the effect is not comparable to that of intranasal corticosteroids (12, 13).

The prophylactic effect of oral H1-antihistamines has been suggested (14) but never demonstrated in clinical trials.

These drugs are also effective in the relief of symptoms of allergic conjunctivitis,

They reduce cough (15, 16) and throat clearing.

Although they have limited efficacy in asthma (17), they cause no harm for this condition. In some studies, it was found that oral H1-antihistamines alone (often at a dose higher than the registered one) or in combination with decongestants had some effect in seasonal asthma associated with rhinitis (18, 19).

A study suggests that cetirine may have a role in the prevention of the onset of asthma (20) but more data are needed.

Safety:

The most troublesome side effect of first-generation H1-antihistamines is sedation (21, 22). This can be defined as a global impairment of psychomotor performance and, subjectively, as a proclivity to fall asleep. Unfortunately, sedation and impairment are not invariably linked. Some individuals do not feel sedated, but are impaired. The second-generation H1-antihistamines are in general less likely to cause sedation (23).

A major concern has been the arrhythmogenic action and associated fatalities have been exceptionally caused by terfenadine, astemizole and high doses of diphenhydramine (24). The cardiac effects relate to the binding affinity for a K channel, -iK_r, a potassium inward rectifying current coded by the human ether go-go related gene (HERG). Although this K channel has high homology with the H1-receptor (5), the prolongation of the QT interval is not class effect, and, is mostly associated with terfenadine and astemizole. These drugs have been withdrawn in many countries because of these serious adverse effects.

Most, if not all, older, classical H1-antihistamines possess pharmacologic effects that are not related to H1-blockade (24). Many first-generation H1-antihistamines block cholinergic muscarinic receptors in a dose-dependent manner. Due to their anti-cholinergic effect, the first generation H1-antihistamines often caused dry mouth, tachycardia, urinary retention and blurred near vision.

The side effects of decongestants are present when H1-antihistamines are combined with a decongestant.

Specific problems of the class:

None.

Requirements for the class:

Several properties should be met by oral H1-antihistamines in development:

Pharmacologic properties:
- potent and selective H1 receptor blockade,
- additive anti-allergic activities (see below),
  - No clinically relevant pharmacokinetic interference by foods, medications or intestinal transport proteins,
  - no known interaction with cytochrome P4503A (CYP3A),
  - no known interaction with disease to avoid toxic reactions.

Efficacy:
- effective in the treatment of intermittent and persistent rhinitis as defined in the ARIA document (25).
- effective for all nasal symptoms including nasal obstruction,
- improvement of eye symptoms,
- if a claim for asthma is made:
  - improvement of asthma symptoms (short term studies),
  - reduction of asthma exacerbations (long term studies),
  - an improvement of the pulmonary function tests, even though in pollen-induced bronchial symptoms, FEV_1 and peak flow rates are usually not altered.
- if a claim for a preventive effect is proposed, appropriate trials should be conducted.
- Studies should be carried out in young children and elderly patients to assess efficacy.

Side effects:
- no sedation or cognitive or psychomotor impairment,
- no anti-cholinergic effects,
- no weight gain,

– no cardiac side effects,
– possible use in pregnancy and breast feeding
– Studies should be carried out in young children and elderly age patients to assess safety.
– Prospective post-marketing safety analyses should be conducted.

Pharmacodynamics:
– rapid onset of action,
– long duration of action, at least persistence of clinical effects at the end of the 24-hour dosing period, so the drug can be administered once a day,
– no likelihood of development of tolerance (tachyphylaxis).

Comparison with other drugs used to treat rhinitis (conjunctivitis):

2-Anti-allergic effects of H1-antihistamines:

Histamine is not the only mediator released during allergic reactions (26, 27). Even though oral H1-antihistamines differ in their relative H1 antagonism, it is usually impossible to differentiate the clinical efficacy in the treatment of nasal, ocular or skin symptoms of these drugs when they are compared in placebo-controlled clinical trials. Changes in skin test reactivity induced by oral H1-antihistamines do not correlate with symptoms during nasal challenge or the pollen season (28).

It appears that oral H1-antihistamines may have additional properties to H1 blockade, and these are called "anti-allergic effects". These properties differ depending on the molecule or the target organ. They can be demonstrated *in vitro*, in animal and in human studies (for review see (3, 7)).

Much of the so-called anti-allergic effect of the drugs is due to stabilization of the inactive form of the receptor. Even in the absence of its agonist, histamine, the H1 receptor exists in two forms, active and inactive. The active state upregulates NF-kappaB which in turn will migrate to the cell nucleus and affect transcription and therefore production of many pro-inflammatory mediators such as ICAM-1, VCAM-1, iNOS, IL-6 or GM-CSF. Anti-histamines stabilise the inactive form of the receptor and thereby will have a number of receptor dependent anti-inflammatory effects. There are, however receptor-independent effects including inhibition of release of some mast cell mediators perhaps by competitive inhibition of the binding of calcium and there seem to be true anti-allergic effects unrelated to the H1-receptor blockade.

In vitro, H1-antihistamines are able to block mediator release from basophils and human mast cells and to reduce the activation markers of some cells such as eosinophils. The concentrations required to achieve the effects are often high, in the micro-molar range. Using new tools of molecular biology, it is possible to demonstrate that the anti-allergic effect is independent of the H1-receptor.

These anti-allergic effects can be seen *in vivo* in skin, nasal and ocular challenge studies in man. Oral H1-antihistamines were found to reduce the release of pro-inflammatory mediators, adhesion molecules such as ICAM-1, and, for some molecules the recruitment of inflammatory cells. Doses required to achieve these effects however, were often greater than those recommended for therapeutic use. Studies in bronchial samples were inconsistent.

Some of these anti-allergic effects were confirmed by clinical trials carried out during the pollen season (29) or natural exposure to house dust mites (30) and in chronic asthma as a steroid-sparring effect (31). Doses required to achieve these effects were however sometimes greater than those recommended.

The clinical relevance of these anti-allergic effects remains to be understood.

It is proposed to ascribe an "anti-allergic effects" to oral H1-antihistamines possessing the following properties:

Any claim for additive anti-allergic properties should be linked to a clinical benefit for the patient for the treatment of allergic symptoms (e.g. corticosteroid sparring effect in asthma).

A mechanistic explanation of the anti-allergic effect should be added.
– reduction in the levels of pro-inflammatory mediators, adhesion molecules or cytokines in nasal or ocular secretions,
– and/or reduction in the number of inflammatory cells in the skin, nasal or ocular tissues,
– During challenge or natural allergen exposure (i.e. pollen season, natural mite exposure),
– At the recommended dose.
– Assessment anti-allergic properties for combinations (with decongestants or anti-leukotrienes).

3-Intra-nasal glucocorticosteroids:

Definition:

Glucocorticosteroids are currently the most efficacious medication available for the treatment of allergic and non-allergic rhinitis. The effect of intra-nasal glucocorticosteroids is based on local activity; the administration of the equivalent amount of drug orally produces no benefit. The rationale for using intra-nasal glucocorticosteroids in the treatment of allergic rhinitis is that high drug concentrations can be achieved at receptor sites in the nasal mucosa, with minimal risk of systemic adverse effects.

Pharmacological properties:

Glucocorticosteroids can suppress many stages of the allergic inflammatory process. This may explain their potent effect on symptoms of allergic rhinitis (32).

Many cells and cytokines playing an active role in allergic inflammation in the nose are influenced by intranasal glucocorticosteroid treatment (32).

The effect of glucocorticosteroids is caused by binding to a single glucocorticoid receptor, which is predominantly localised to the cytoplasm of target cells. After binding of the glucocorticoid, the complex moves to the nuclear compartment where it increases or inhibits gene transcription through a process known as transactivation and transrepression respectively (33).

Pharmacokinetics:

Due to their mechanism of action, glucocorticosteroids have a slow onset of action and need a few hours to be effective. They appear to demonstrate efficacy after 7 hours of treatment but their maximum efficacy may require up to 2 weeks.

Until recently, it was thought that there was a need for a regular treatment which was found to be more effective than a prn one (34). However, recent studies show that they can be administered as required and show similar or better efficacy than oral H1-antihistamines (35).

Efficacy:

In intermittent or persistent allergic rhinitis, intra-nasal glucocorticosteroids very effectively control nasal symptoms in the majority of patients (for review see (3)).

They are effective for all nasal symptoms including nasal blockage.

However, not all patients benefit equally from the treatment. Failure to treatment will frequently be due to failure to take the treatment on a regular basis, or, equally important, failure to use the nasal spray correctly or local side effects.

The prophylactic effect of intra-nasal glucocorticosteroids has been suggested in clinical trials (36).

Intranasal corticosteroids are effective within hours but their full efficacy is reached after 2 weeks of treatment.

As required (prn) medication appears to be a treatment option but more data are needed.

A once-daily administration is possible with most drugs.

Intra-nasal glucocorticosteroids are equally or more effective than oral H1-antihistamines in rhinitis (37).

They are more effective than topical cromones.

They are partially effective for eye symptoms.

They may improve asthma symptoms and exacerbations.

In all guidelines on the management of rhinitis, intranasal glucocorticosteroids were considered first-line therapy in moderate to severe cases of persistent allergic rhinitis in adults (3).

Safety:

Local side effects: The current intra-nasal preparations are well tolerated. Crusting, dryness and minor epistaxis may occur in 5-10% or patients, occasionally persistent and a reason for withdrawal of the product.
Intranasal corticosteroids can be used on a long-term basis without atrophy of the mucosa (38–40).
Hypothalamic-pituitary-adrenal (HPA) axis suppression: Systemic absorption may occur following inhaled and intra-nasal administration of glucocorticosteroids, but patients receiving only intra-nasal glucocorticosteroids appear to be at very low risk of developing HPA axis suppression because of the low doses required (41). More studies are needed to fully appreciate the effect of combined intra-nasal and intra-bronchial glucocorticosteroids, in particular in children.

Other side effects such as skin thinning, increased cataract formation, glaucoma, metabolic changes and behavioural abnormalities may be observed with inhaled (bronchial route) glucocorticosteroids. However, they do not appear to be present in patients receiving only intranasal glucocorticosteroids.

In children, growth retardation has been observed for beclomethasone administered over a year by intra-nasal route (42). However, studies with other molecules did not find this side effect. From the studies of inhaled glucocorticosteroids in asthma, longer treatment was not associated with growth effects. The same may apply for intra-nasal corticosteroids (43).

In children, the impact of cumulative doses of intranasal and inhaled corticosteroids administered to the same patient needs to be considered. Moreover, many children with concomitant atopic dermatitis require skin applications of corticosteroids.

There are very few documented studies with intra-nasal glucocorticosteroids during pregnancy (44).

Specific problems of the class: none.

Requirements for the class:

Several properties should be met by intra-nasal glucocorticosteroids in development:

Pharmacologic properties:
- potent action on transcription factors,
- first pass hepatic metabolism,

Efficacy:
- effective in the treatment of intermittent and persistent rhinitis as defined in the ARIA document (25).
  - effective for all nasal symptoms,
  - improvement of eye symptoms,

– if a claim for asthma is proposed:
  – improvement of asthma symptoms (short term studies)
  – reduction of asthma exacerbations (long term studies)
  – an improvement of the pulmonary function tests, even though in pollen-induced bronchial symptoms, FEV_1 and peak flow rates are usually not altered.
– if a claim for nasal polyposis or sinusitis is proposed, the adequate appropriate trials should be conducted
– if a claim for a preventive effect is proposed, appropriate trials should be conducted.

Side effects:
– minimal local side effects
– no HPA axis effects
  – especially in children
  – and in association with the inhaled (intra-bronchial) form
– no long term effect on growth in children
– possible use in pregnancy

Pharmacodynamics:
– assessment of the onset of action,
– long duration of action, at least 24 hr, ability to be administered once a day,
– if a claim for a prn use is proposed, additional appropriate trials should be conducted.

Comparison with other drugs used to treat rhinitis:

Jean Bousquet
Service des Maladies Respiratoires
CHU Montpellier
34295- Montpellier-Cedex 05
France
phone: 00-33-467-33-61-05
E-mail: jean.bousquet@wanadoo.fr

References

1. International Consensus Report on Diagnosis and Management of Rhinitis. International Rhinitis Management Working Group. Allergy 1994; **49**(19 Suppl):1–34.
2. Van Cauwenberge P, Bachert C, Passalacqua G, Bousquet J, Canonica GW, Durham SR et al. Consensus statement on the treatment of allergic rhinitis. European Academy of Allergology and Clinical Immunology. Allergy 2000;**55**(2):116–134.
3. Bousquet J, Van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. J Allergy Clin Immunol 2001;**108**(5 Suppl):S147–S334.
4. Simons FE, Simons KJ. Clinical pharmacology of H1-antihistamines. Clin Allergy Immunol 2002;**17**:141–178.
5. Leurs R, Church MK, Taglialatela M. H1-antihistamines: inverse agonism, anti-inflammatory actions and cardiac effects. Clin Exp Allergy 2002;**32**(4):489–498.
6. Bousquet J, Lebel B, Chanal I, Morel A, Michel FB. Antiallergic activity of H1-receptor antagonists assessed by nasal challenge. J Allergy Clin Immunol 1988;**82**(5 Pt 1):881–887.
7. Canonica GW, Ciprandi G, Passalacqua G. Nonsteroidal antiallergic treatments in allergic rhinitis. Am J Rhinol 2000;**14**(5):319–323.
8. Doherty MM, Charman WN. The mucosa of the small intestine: how clinically relevant as an organ of drug metabolism? Clin Pharmacokinet 2002;**41**(4):235–253.
9. Dresser GK, Bailey DG, Leake BF, Schwarz UI, Dawson PA, Freeman DJ et al. Fruit juices inhibit organic anion transporting polypeptide-mediated drug uptake to decrease the oral availability of fexofenadine. Clin Pharmacol Ther 2002;**71**(1):11–20.
10. Renwick AG. The metabolism of antihistamines and drug interactions: the role of cytochrome P450 enzymes. Clin Exp Allergy 1999;**3**:116–124.
11. Simons FE. H1-antihistamines in children. Clin Allergy Immunol 2002;**17**:437–464.
12. Nayak AS, Schenkel E. Desloratadine reduces nasal congestion in patients with intermittent allergic rhinitis. Allergy 2001;**56**(11):1077–1080.
13. Ciprandi G, Cosentino C, Milanese M, Mondino C, Canonica GW. Fexofenadine reduces nasal congestion in perennial allergic rhinitis. Allergy 2001;**56**(11):1068–1070.
14. Dolovich J, Moote DW, Mazza JA, Clermont A, PetitClerc C, Danzig M. Efficacy of loratadine versus placebo in the prophylactic treatment of seasonal allergic rhinitis. Ann Allergy 1994;**73**(3):235–239.
15. Ciprandi G, Buscaglia S, Catrullo A, Marchesi E, Bianchi B, Canonica GW. Loratadine in the treatment of cough associated with allergic rhinoconjunctivitis. Ann Allergy Asthma Immunol 1995;**75**(2):115–120.
16. Ciprandi G, Tosca M, Ricca V, Passalacqua G, Fregonese L, Fasce L et al. Cetirizine treatment of allergic cough in children with pollen allergy. Allergy 1997;**52**(7):752–754.
17. Van-Ganse E, Kaufman L, Derde MP, Yernault JC, Delaunois L, Vincken W. Effects of antihistamines in adult asthma: a meta-analysis of clinical trials. Eur Respir J 1997;**10**(10):2216–2224.
18. Grant JA, Nicodemus CF, Findlay SR, Glovsky MM, Grossman J, Kaiser H et al. Cetirizine in patients with seasonal rhinitis and concomitant asthma: prospective, randomized, placebo-controlled trial. J Allergy Clin Immunol 1995;**95**(5 Pt 1):923–932.
19. Corren J, Harris AG, Aaronson D, Beaucher W, Berkowitz R, Bronsky E et al. Efficacy and safety of loratadine plus pseudoephedrine in patients with seasonal allergic rhinitis and mild asthma. J Allergy Clin Immunol 1997; **100**(6 Pt 1):781–788.

20. Warner JO. A double-blinded, randomized, placebo-controlled trial of cetirizine in preventing the onset of asthma in children with atopic dermatitis: 18 months' treatment and 18 months' posttreatment follow-up. J Allergy Clin Immunol 2001;**108**(6):929–937.
21. Passalacqua G, Scordamaglia A, Ruffoni S, Parodi MN, Canonica GW. Sedation from H1 antagonists: evaluation methods and experimental results. Allergol Immunopathol Madr 1993;**21**(2):79–83.
22. Welch MJ, Meltzer EO, Simons FE. H1-antihistamines and the central nervous system. Clin Allergy Immunol 2002;**17**:337–388.
23. Timmerman H. Why are non-sedating antihistamines non-sedating? Clin Exp Allergy 1999;**3**:13–18.
24. Passalacqua G, Bousquet J, Bachert C, Church MK, Bindsley-Jensen C, Nagy L et al. The clinical safety of H1-receptor antagonists. An EAACI position paper. Allergy 1996;**51**(10):666–675.
25. Bousquet J, VanCauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma (ARIA)- Executive summary. Allergy 2002;**57**(9):841–855.
26. Howarth PH, Salagean M, Dokic D. Allergic rhinitis: not purely a histamine-related disease. Allergy 2000; **55**(Suppl 64):7–16.
27. Naclerio RM. Pathophysiology of perennial allergic rhinitis. Allergy 1997;**52**(36 Suppl):7–13.
28. Bousquet J, Czarlewski W, Cougnard J, Danzig M, Michel FB. Changes in skin-test reactivity do not correlate with clinical efficacy of H1-blockers in seasonal allergic rhinitis. Allergy 1998;**53**(6):579–585.
29. Ciprandi G, Passalacqua G, Mincarini M, Ricca V, Canonica GW. Continuous versus on demand treatment with cetirizine for allergic rhinitis. Ann Allergy Asthma Immunol 1997;**79**(6):507–511.
30. Ciprandi G, Tosca M, Ricca V, Passalacqua G, Riccio AM, Bagnasco M et al. Cetirizine treatment of rhinitis in children with pollen allergy: evidence of its antiallergic activity. Clin Exp Allergy 1997;**27**(10):1160–1166.
31. Busse WW, Middleton E, Storms W, Dockhorn RJ, Chu TJ, Grossman J et al. Corticosteroid-sparing effect of azelastine in the management of bronchial asthma. Am J Respir Crit Care Med 1996;**153**(1):122–127.
32. Fokkens WJ, Godthelp T, Holm AF, Klein-Jan A. Local corticosteroid treatment: the effect on cells and cytokines in nasal allergic inflammation. Am J Rhinol 1998;**12**(1):21–26.
33. Adcock IM, Caramori G. Cross-talk between pro-inflammatory transcription factors and glucocorticoids. Immunol Cell Biol 2001;**79**(4):376–384.
34. Juniper EF, Guyatt GH, Archer B, Ferrie PJ. Aqueous beclomethasone dipropionate in the treatment of ragweed pollen- induced rhinitis: further exploration of "as needed" use. J Allergy Clin Immunol 1993;**92**(1 Pt 1):66–72.
35. Kaszuba SM, Baroody FM, deTineo M, Haney L, Blair C, Naclerio RM. 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): 2581–2587.
36. Graft D, Aaronson D, Chervinsky P, Kaiser H, Melamed J, Pedinoff A 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):724–731.
37. 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): 1624–1629.
38. Minshall E, Ghaffar O, Cameron L, O'Brien F, Quinn H, Rowe-Jones J 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):648–654.
39. Holm AF, Fokkens WJ, Godthelp T, Mulder PG, Vroom TM, Rijntjes E. 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.
40. Laliberte F, Laliberte MF, Lecart S, Bousquet J, Klossec JM, Mounedji N. Clinical and pathologic methods to assess the long-term safety of nasal corticosteroids. French Triamcinolone Acetonide Study Group. Allergy 2000;**55**(8):718–722.
41. Perry RJ, Findlay CA, Donaldson MD. Cushing's syndrome, growth impairment, and occult adrenal suppression associated with intranasal steroids. Arch Dis Child 2002;**87**(1):45–48.
42. Skoner D, Rachelefsky G, Meltzer E, Chervinsky P, Morris R, Seltzer J et al. Detection of growth suppression in children during treatment with intranasal belcomethasone dipropionate. Pediatrics 2000;**105**:e23.
43. Pedersen S. Assessing the effect of intranasal steroids on growth. J Allergy Clin Immunol 2001;**108**(1 Suppl): S40–S44.
44. Ellegard EK, Hellgren M, Karlsson NG. Fluticasone propionate aqueous nasal spray in pregnancy rhinitis. Clin Otolaryngol 2001;**26**(5):394–400.