REVIEW

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Nasal inflammation and anti-inflammatory treatment. Semantics or clinical reality?*

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SUMMARY

In recent years there has been a tremendous development in molecular biology and with that an improved understanding of the immunological and inflammatory background for rhinitis. However, this progress has not yet had any influence on diagnosis or choice of treatment. Today it is emphasized that allergic rhinitis is an inflammatory disease. However, the majority of allergic rhinitis symptoms are caused by histamine, which can be released from a non-inflamed mucous membrane. Thus, the role of inflammation may be overestimated as a cause of rhinitis symptoms. It is often claimed that the 2nd generation antihistamines have non-H1 mediated anti-inflammatory effects of clinical significance. However, the large majority of published clinical data speaks against this hypothesis. Corticosteroids do not, as often believed have a general anti-inflammatory effect in the nose. They are highly effective in a disease associated with eosinophil-dominated inflammation (e.g. allergic rhinitis), but not in a disease associated with neutrophil-dominated inflammation (e.g. the common cold). It is recommended that drugs are used merely based on a thorough cost-risk-benefit-patient-compliance analysis in the single patient and disease entity with little attention being paid to the assumed mode of action of the drug, which may or may not be of clinical relevance.

Key words: rhinitis, inflammation, anti-inflammatory treatment, corticosteroids, anti-histamines.

INTRODUCTION

Probably, most readers of this journal will agree in the following statement: "Rhinitis is an inflammatory disease requiring anti-inflammatory treatment". Semantically, the statement is correct, as "rhinitis" means inflammation of the nose, and anti-inflammatory therapy aims at normalizing this basic pathological condition.

In clinical practice, however, the above statement is an over-simplification which associates symptoms and their treatment in a way that may not be correct in all patients presenting with sneezing, rhinorrhea and nasal blockage.

DEFINITION OF INFLAMMATION

Classical inflammation

The word inflammation is derived from "inflammare", which is latin for "to set on fire". Inflammation was originally defined, based on symptoms and signs, as "rubor, dolor, calor, tumor and functio laesa" (Dorland's Illustrated Medical Dictionary). In clinical practice it does not make sense to use this definition for rhinitis, as it means "a swollen, red, warm and painful nose, which is out of order".

Histological inflammation

Based on ordinary light microscopy, inflammation is characterized by "dilatation of arterioles, capillaries, and venules, with increased permeability and blood flow; exudation of fluids, including plasma proteins; and leukocyte migration into the inflammatory focus" (Dorland's Illustrated Medical Dictionary). A diagnosis of "histological inflammation" can be made provided the physician performs a histological or a cytological examination of the nose, but this is rarely done in daily clinical work (Lund et al., 1994).

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Molecular inflammation
The magnificient advances in molecular biology, in recent years, have fundamentally changed the definition of inflammation and have made it highly sofisticated. Inflammation of the nasal mucosa can now be characterized, for example, by an increase in the number of a lymphocyte subset, characterized by a specific CD-numbered molecule in the cell membrane. It can also be a sign of inflammation that an increased expression of an adhesion molecule on endothelial or epithelial cells can be demonstrated by immunohistochemistry or by an *in situ* hybridisation technique. In addition, inflammation can be shown by an increased level of a mediator, a cytokine or a chemokine in nasal lavage fluid or in a mucosal biopsy (Christodoulopoulos et al., 2000). Such diagnostic methods are used in the research laboratory but not in the clinician's daily work.

Definition of rhinitis
Neither the presence of "classical inflammation", "histological inflammation" nor "molecular inflammation" can be used for the definition, classification and diagnosis of rhinitis in clinical practice, or for the choice of treatment. Although it is unsatisfactory, we are at present confined to use a symptomatic diagnosis of rhinitis as a disease characterized by sneezing, rhinorrhea and nasal blockage.

Inflammation and rhinitis
The causal relationship between inflammation and rhinitis symptoms is far less clear than commonly believed. In fact, there is very little evidence that the upregulation of any inflammatory marker directly results in sneezing, rhinorrhea and nasal blockage. At present, the clinical significance of molecular inflammatory events remains largely speculative.

Langerhans cells and Th2 cells
These cells, of primary importance for sensitization and antigen-presentation, are found in an increased number in the allergic nasal mucosa (Holm et al., 1995; Christodoulopoulos et al., 2000).

Cytokines, chemokines and adhesion molecules
This is not the place for reviewing the steadily mushrooming number of cytokines, chemokines and adhesion molecules, having peculiar acronyms as names, such as "Regulated upon Activation Normal T cell Expressed and Secreted" (RANTES). It suffices to say that, by a united effort, all these molecules, sequentially upregulated and downregulated, succeed in convincing the eosinophils to invade the entire nasal mucosa, and they wellcome mast cells to the epithelial lining, close to the encounter of inhaled allergens.

Mediators
No doubt, histamine is by far the most important mediator of allergic rhinitis. Histamine can induce all rhinitis symptoms with the exception of hyper-responsiveness (Grønborg et al., 1986). In contrast to common believe, measurement of histamine in nasal lavage fluid is not a reliable measure of an allergic reaction, as the histamine concentration parallels the glandular secretory activity (Jacobi et al., 1998). The slight clinical effect of cysteinyl leukotriene antagonists in allergic rhinitis (Mygind et al., 2000) indicates that leukotrienes play a small clinical role. On the other hand, the apparent lack of clinical effect of NSAIDs indicates that prostaglandins do not play any significant role.

Mast cells
The only consequence of inflammation which, with a high degree of probability, is directly related to the expression of rhinitis symptoms, is the increased number of epithelial mast cells, causing an increased capacity for histamine release (Meltzer et al., 1990).
During the pollen season, the symptom response to a nasal provocation with allergen increases about 300% (Borum et al., 1983). As the same increase in responsiveness occurs with a histamine provocation it indicates that an increased responsiveness of sensory nerves is more important than is an increased number of epithelial mast cells.

Eosinophils
Mucosal eosinophilia is a hallmark of asthma and allergic rhinitis. In asthma, it is generally assumed, and highly likely, that eosinophil cytotoxic proteins contribute to epithelial damage and the development of hyper-responsiveness. In allergic rhinitis, however, the epithelial lining is intact, and hyper-responsiveness is a clinically less important manifestation in the nose than in the bronchi (Gerth van Wijk, 1987). In allergic rhinitis, the evidence that eosinophil products are the cause of hyper-responsiveness is merely circumstantial (Klementsson et al., 1990), and there are no data to show a causal relationship between eosinophils and symptoms.

THE SYMPTOMS OF RHINITIS
Although, being in the periphery of the actual issue, it may be of interest to analyse the mechanisms of how symptoms are generated in allergic rhinitis.

Sneezing
Histamine challenge of the nose gives, within seconds, the typical "hay-fever sensation" with intense itching or tickling in the nose, followed by sneezing within a minute (Kirkegaard et al., 1983). No other mediators, including leukotrienes and prostaglandins have this effect on sensory nerves (Mygind et al., 2000). These symptoms can effectively be blocked by pretreatment with a 1st and a 2nd generation H_1 antihistamine.

Rhinorrhea - mucus production
Mucus is produced, to a small amount, by goblet cells in the surface epithelium, and to a much higher degree by submucosal glands, which predominantly are stimulated by a parasympathic pathway, but probably also to a slight degree by secretagogues, such as cysteinyl leukotrienes (Mygind et al., 2000). The almost complete inhibition of allergen-induced rhinorrhea from pretreatment with a cholinoceptor antagonist (Konno et al., 1983)

is strongly suggestive of a parasympathetic reflex as the dominating cause of rhinorrhea, which is probably induced by an effect of histamine on sensory nerves.

Nasal blockage

Nasal blockage is mainly due to vasodilatation and not to plasma exudation and oedema formation, as shown by the marked effect obtained with vasoconstrictors in rhinitis. Some blood vessels contract and others dilate upon allergen challenge and in allergic rhinitis, causing the typical pale-bluish colour of the nasal mucous membrane. Blood vessels also increase their permeability due to release of mediators from inflammatory cells. The importance of histamine also for this symptom, is indicated by the pronounced nasal blockage induced by a histamine challenge (Secher et al., 1982). The fact that antihistamines have little effect on allergen-induced blockage, may be explained in two ways. First, by the significance of H_2 receptors. This is supported by some effect of an H_2 antihistamine, and by the observation that H_1 antihistamines only have a partial inhibitory effect on histamine-induced nasal blockage (Secher et al., 1982). Second, it seems likely that also other mediators are of importance for nasal blockage. However, a nasal challenge with, for example, cysteinyl leukotrienes merely induces a slight increase in nasal airway resistance, and in blood flow (Bisgaard et al., 1983).

IS HISTAMINE RELEASE OR INFLAMMATION THE CAUSE OF NASAL SYMPTOMS?

A distinction between histamine release and inflammation as the cause of nasal symptoms is made because a mucous membrane, showing no signs of inflammation, is able to release histamine from IgE-sensitized mast cells, and thereby induce sneezing, rhinorrhea and nasal blockage.

Below will be described two situations, having a high and a low ratio between the clinical significance of acute histamine effects and of chronic inflammation. The analysis will be confined to sneezing which, admittedly, is the symptom assumed to have the best correlation between histamine release and inflammation.

Allergen provocation with pollen outside the season

In a recent study (Jacobi et al., 2000), we challenged pollen-allergic volunteers outside the season after pretreatment with the H_1 antihistamine, cetirizine and with placebo.

The results showed that the number of sneezes was 10 times higher during the early-phase response (0-1 h) than during the total late-phase response (2-8 hours), showing that sneezing is a major symptom of the early- and not of the late-phase response to allergen.

While the mean number of sneezes was 30 after placebo pretreatment it decreased dramatically to 3.0 following cetirizine pretreatment. These few sneezes include non-histamine mediated sneezing, unspecific sneezing from the spraying procedure and possibly lack of compliance to medication. Thus, it can be concluded that in this situation at least 90% of all sneezes is due to an acute effect of histamine.

Daily chronic allergen exposure

In a placebo-controlled trial (Wihl et al.,1985), we studied patients with chronic perennial allergic rhinitis with regard to the effect of the H_1 antihistamine, astemizole alone and in combination with the nasal corticosteroid, beclomethasone dipropionate. Sixty per cent of all sneezes responded to antihistamine treatment and, consequently, were caused by histamine release. Only 25% of the sneezes were exclusively responsive to corticosteroid, while 15% were unresponsive to pharmacotherapy.

This study showed that even in chronic perennial allergic rhinitis, mast cell degranulation and histamine release plays a relatively more important role in inducing sneezing than does inflammation *per se.*

ANTI-INFLAMMATORY TREATMENT

Are corticosteroids generally anti-inflammatory?

Nasal corticosteroid treatment has a multitude of anti-inflammatory effects. It reduces the number of T lymphocytes (Rak et al., 1994), Langerhans' cells (Holm et al., 1995) epithelial mast cells and with that the capacity for histamine release (Mygind and Lund, 1996). Also the number of eosinophils is reduced, and there are data indicating a positive correlation between the number of eosinophils in the nose and the response to corticosteroids (Balle et al., 1980; Small et al., 1982).

At present it cannot be explained why pretreatment with corticosteroids can half the number of sneezes following allergen provocation of pollen-allergic volunteers outside the season (Mygind et al., 1977), because corticosteroids do not appear to have any effect on mast cell releasability. It also seems unlikely that the marked effect of corticosteroids on sneezing in allergic rhinitis exclusively is due to the ability to reduce the number of epithelial mast cells. Thus, although corticosteroids are known to be anti-inflammatory, we cannot completely explain how they reduce rhinitis symptoms.

If rhinitis is defined as inflammation of the nasal mucosa, based upon upregulation of cytokines, chemokines and adhesion molecules, then almost all nasal diseases (allergic rhinitis, non-allergic rhinitis, common cold, bacterial rhinosinusitis, Wegener's granulomatosis, primary ciliary dyskinesia, atrophic rhinitis, lepra, etc.) are inflammatory diseases. Even touching the nasal mucosa induces neutrophilia and inflammation (Winther et al., 1984).

Obviously, it is incorrect to treat all these inflammatory diseases with anti-inflammatory drugs. While corticosteroids are highly effective in allergic rhinitis and in other types of rhinitis, characterized by eosinophil-dominated inflammation, such as nasal polyposis, controlled trials have documented that they have little or no effect in rhinovirus-induced rhinitis and in chronic infectious rhinosinusitis, which are diseases characterized by a neutrophil-dominated inflammation (Puhakka et al., 1998). Thus, even corticosteroids cannot be considered as generally anti-inflammatory.

An example of how a wrong conclusion can be made if a direct link is drawn from corticosteroid effect on "molecular inflam-

mation“ and to rhinitis symptoms was nicely shown by Wytske Fokkens and her group in Rotterdam (Holm et al., 1995).
They showed that the number of antigen-presenting Langerhans' cells in the nasal mucosa is increased following an allergen provocation and in perennial rhinitis. This “molecular inflammation“ was completely inhibited by treatment with a nasal corticosteroid. However, in these perennial rhinitis patients, the anti-inflammatory corticosteroid had no effect on the nasal symptoms.

Are antihistamines anti-inflammatory?
It is often stated that the 2nd generation antihistamines are not merely H_1-receptor antagonists but that they also have non-H_1 mediated anti-inflammatory effects (Bousquet et al., 1995). For example, it is claimed that inhibition of antigen-induced upregulation of ICAM-1 by treatment with the antihistamine, cetirizine means that the drug has a clinically useful anti-inflammatory effect, because it inbibits cell recruitment, especially of eosinophils (Kaiser, 1995). First, there is no evidence that eosinophilia directly results in rhinitis symptoms (Klementsson et al., 1990). Second, cetirizine does not reduce the number of eosinophils in the allergen-challenged nose (Jacobi et al., 2000).
If an antihistamine has non-H_1 anti-inflammatory properties of clinical significance - then it must be demonstrated to have the following clinical effects. (1) Be more effective than 1st generation antihistamines. (2) Have a significant effect on nasal blockage, measured by an objective method. (3) The manufacturer should not find it necessary to add a vasoconstrictor. (4) Have a significant effect on late-phase response. (5) Have a significant effect on nasal hyperresponsiveness. (6) Have an effect on the number of epithelial mast cells and on epithelial/mucosal eosinophils. (7) Have an effect of nasal symptoms for days after medication is stopped. (8) Be effective in nasal polyposis. (9) Have a better effect on asthma/bronchial hyperresponsiveness than 1st generation antihistamines. (10) Have an effect on atopic dermatitis.
The large majority of published data and clinical experience speaks against antihistamines fulfilling these criteria. On the other hand, all these requirements are met by corticosteroids which invariably are more effective than antihistamines, when compared in controlled trials (Stempel & Thomas, 1998; Weiner et al., 1998). Thus, there is very little clinical evidence that the 2nd generation antihistamines have any other clinical effects than an H_1-receptor blocking activity. In my opinion, all clinically effects of antihistamines can be explained based on blockage of the H_1 receptor, and “an antihistamine is an antihistamine is an antihistamine“, and it needs not to be ashamed of that.
Finally, the effect of adding an antihistamine to a nasal corticosteroid is marginal and it could not be detected in 4 double-blind studies of 1,250 rhinitis patients (Juniper et al., 1989; Simpson et al., 1994; Benincasa et al., 1994; Ratner et al., 1998). This is amazing, considering the important role, played by histamine, and the mediocre effect of corticosteroids on histamine release and effects. There are still a number of unanswered questions about rhinitis, inflammation and therapy.

THE FUTURE
At present the concept of rhinitis as an inflammatory disease is neither useful for diagnosis nor for treatment. However, it is realistic to believe that a test, based on molecular biology, may be developed for the diagnosis and classification of rhinitis. With regard to treatment, it has for decades been based on nasal corticosteroids and antihistamines, but it does not seem possible further to develop this pharmacotherapeutic approach. It is more likely that the next break-through in anti-rhinitis treatment will be based on the development of more specific anti-inflammatory therapy with antagonists and antibodies to important receptors and pro-inflammatory cytokines. In the near future, a new therapeutic principle, consisting of anti-IgE antibodies, will be introduced.

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