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The Use of Antiallergic and Antiasthmatic Drugs in Viral Infections of the Upper Respiratory Tract

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Summary

Despite their frequency, upper respiratory tract infections (URTIs) constitute an area with few, if any, effective treatment remedies. Asthma and airway allergies share similar pathogenetic mechanisms to URTIs and it is not surprising, therefore, that agents used to treat allergic disorders have also been studied in URTIs. Their possible effects, limitations and hypothetical modes of action in URTIs are reviewed. In controlled clinical trials of satisfactory scientific standard, symptom reductions in both experimental rhinovirus infections and natural colds have occurred with topical anticholinergics, oral antihistamines and topical chromones. Future treatment alternatives for URTIs may include the intranasal anticholinergic ipratropium bromide, new nonsedating antihistamines and sodium cromoglycate (cromolyn sodium). The latter has a record of safety and an absence of adverse effects that would make it an attractive alternative for this common but not particularly serious condition in otherwise healthy individuals.

Upper respiratory tract infections (URTIs) have many common features with asthma and allergic diseases in the respiratory system. The inflammatory mediators are similar in both groups of diseases, and the therapeutic effects of antiallergic or antiasthmatic drugs in URTIs have been used as arguments for the presence of common pathways of inflammatory mediators.[1] This brief review discusses the evidence for these common pathways, and reviews the potential for the use of antiallergic and antiasthmatic drugs in these common but usually trivial infections.

Figure 1 summarises the pathophysiology of rhinovirus infection and the proposed mechanisms of action of antiallergic and antiasthmatic drugs.

1. Pathways and Mediators of Respiratory Tract Inflammation

1.1 Chemical Inflammatory Mediators

Mast cells and histamine are probably not involved in the ordinary common cold,[2,3] as they may be in lower respiratory tract infections with bronchiolitis,[4] but there are many other possible mediators likely to play a role. For example, a potent proinflammatory cytokine, tumour necrosis factor-α (TNFα), is often present in nasal mucosa in URTIs.[5] In a study of cytokines in nasal secretion,[6] the concentration of interferon-γ (IFNγ) increased with symptoms in coronavirus-induced cold

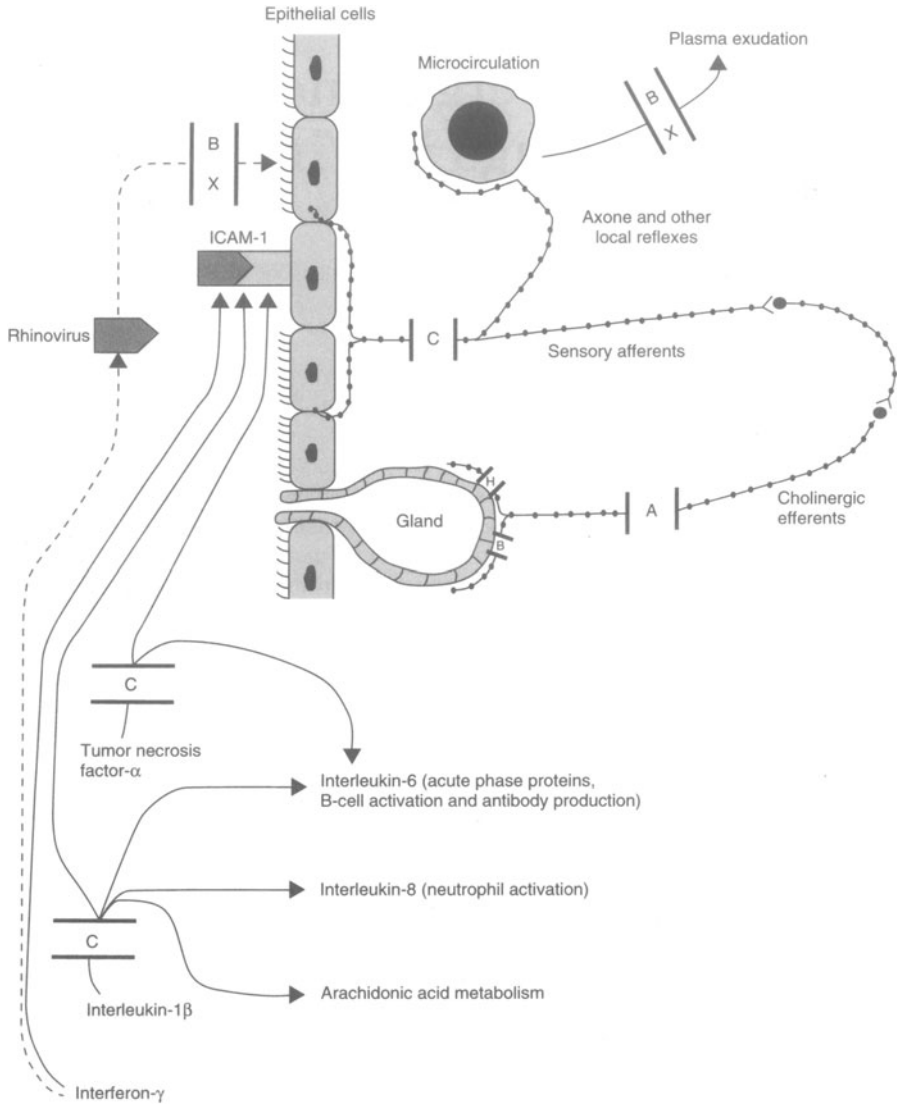

Fig. 1. Schematic view of the pathophysiology of inflammation and the proposed actions of drugs in rhinovirus infection. Corticosteroids (not included) inhibit most mediators and plasma exudation, as well as activation of inflammatory cells. Enhancement and inhibition in pathophysiology are shown by solid and broken lines, respectively. The sites of action of anticholinergics (A), β_2-agonists (B), chromones (mast cell stabilisers) [C], antihistamines (H) and xanthines (X) are indicated. *Abbreviation:* ICAM-1 = intercellular adhesion molecule-1.

but was not increased in allergic rhinitis after challenge with birch pollen. Granulocyte-macrophage colony-stimulating factor (GM-CSF) was only increased after allergen challenge, but interleukin-1β (IL-1β) was increased in both virus infection and after allergen challenge. In another study of prophylaxis with corticosteroids before and after challenge with rhinovirus,[7,8] IL-1β was increased in nasal lavage in symptomatic patients.

In an *in vitro* study of respiratory epithelial cells, rhinovirus infection caused increased production of interleukin-8 (IL-8), interleukin-6 (IL-6) and

GM-CSF.[9] The production of IL-8 correlated with viral replication during the first 24 hours of infection.

1.2 Autonomic Nervous Regulation

Other pathophysiological mechanisms which might be implicated in URTIs are disturbances of the autonomic nervous system. In his theory of β-adrenergic abnormality in asthma in 1968, Szentivanyi suggested that viral infections exacerbate the functional 'β-blockade' underlying airway abnormalities in asthma.[10] Diminished β-adrenergic function in leucocytes has been shown both in patients during respiratory viral infections[11] and after incubation with virus *in vitro*.[12] The consequence of such changes in leucocytes could translate to increased cell activation and tissue inflammation.

One of the basic pathological changes in bronchial asthma is increased cholinergic sensitivity and activity, with the consequence that the methacholine test is one of the main quantitative tests of bronchial hyperreactivity.[13] Bronchial reactivity is also increased in nonasthmatic individuals during viral respiratory infections,[14] but can be blocked by pretreatment with atropine, indicating a cholinergic upregulation in viral respiratory infections.

Incubation of membrane preparations from guinea-pig lung with parainfluenza virus has indicated that muscarinic M_2 receptors are impaired by the virus infection, and this may explain the increase in vagally mediated bronchoconstriction observed in viral respiratory infections.[15] The M_2 receptor functions as a so-called prejunctional autoreceptor that inhibits acetylcholine release, and a selective loss causes cholinergic activation.[16] In viral infections that injure airway epithelium, such as parainfluenza and influenza, there is an increased activity of, and increased bronchial response to, substance P, a neuropeptide involved in neurogenic bronchoconstriction and neurogenic inflammation.[17-18] Naturally occurring viral infections in rat trachea cause an increased susceptibility to neurogenic inflammation induced by substance P, capsaicin or direct stimulation of the vagal nerve.[19] The effect was seen even in the absence of virus-induced changes such as increased vascular permeability, adherence of neutrophils to blood vessels or influx of neutrophils to the mucosa, and the increased susceptibility to neurogenic inflammation lasted longer than the other pathological changes observed.

1.3 Adhesion Molecules

Cell adhesion molecules are another area of molecular interaction between asthma, allergy and respiratory viral diseases. Adhesion molecules are cellular structures that are involved in the pathogenesis of allergic inflammation and that also act as cellular receptors for viral infections.[20] Intercellular adhesion molecule-1 (ICAM-1) is the cellular receptor for most rhinoviruses and some coxsackie viruses,[21] and may be upregulated by IFNγ and IL-1β in inflamed airway mucosa[20,22,23] and experimentally by TNFα.[9,24] IFNγ is more potent than the other cytokines in enhancing epithelial ICAM-1,[25] but its antiviral effect still makes the epithelium less susceptible to infection with rhinovirus.[9]

Rhinovirus infections have since long been known as the most common trigger of asthma exacerbations in children,[26] and upregulation of ICAM-1 in airway epithelium in subclinical inflammation has been suggested to enhance the susceptibility to rhinovirus in patients with asthma.[20] Drugs that inhibit the upregulation of ICAM-1 may hypothetically hamper the local spread of rhinovirus in the airway mucosa. As asymptomatic infections do not worsen the asthma condition,[26] effective symptomatic treatment of the infection may substantially contribute to the control of asthma symptoms.

2. Drug Effects

Only well controlled studies of high scientific standard are reviewed below. Studies on the use of combinations of drugs are not included, unless they are of principal interest regarding mechanisms.

2.1 Antihistamines

Although histamine is not considered to be involved in URTIs, antihistamines have been widely used in cold remedies for decades. An anticholinergic drying effect on the mucous membranes has

been suggested as the main effect, a conclusion based on the ineffectiveness of terfenadine, one of the second generation antihistamines, against the symptoms of URTIs.[27] On the other hand, more general anti-inflammatory effects than are likely to be derived from H_1 receptor antagonism have been shown for a number of second generation antihistamines.[28]

In a critical review of clinical trials between 1950 and 1991, Smith and Feldman[29] scored 20 studies of antihistamine use in the common cold on 11 criteria to determine scientific validity; 10 of these trials were considered to fill acceptable scientific standards. In 4 studies of an older antihistamine, chlorphenamine (chlorpheniramine), 3[30-32] showed reduction of sneezing, nasal mucus amount or symptom score, and 1 showed no benefit.[33] In only 1 of these studies was drowsiness attributed to the drug.[33] Other older antihistamines, such as thonzylamine,[34] intranasal diphenhydramine[33] and triprolidine hydrochloride,[35] were all no better than placebo in reduction of symptoms. A newer nonsedating antihistamine, terfenadine, reduced nasal symptoms in 1 study using 60mg twice daily,[36] but failed to do so in another using 60mg twice daily[27] and in one using 120mg twice daily.[37]

If the new generation nonsedating antihistamines could cause substantial reduction of symptoms in URTIs, they would offer an attractive choice of treatment. Administration is convenient and the drugs are relatively free from adverse effects at the recommended dosages.[38]

2.2 Chromones

The chromone ('mast cell stabiliser') group includes 2 clinically used drugs, sodium cromoglycate (cromolyn sodium) and nedocromil. They have similar antiallergic and anti-inflammatory properties,[39] and exert their effect on mast cells, eosinophils, epithelial cells and sensory nerves.[40-42] Their basic mode of action is probably inhibition of chloride channels involved in inflammatory responses in the airways, resulting in inhibition of a wide scope of chemical inflammatory mediators as well as inhibitory effects on sensory fibres.[43] Both drugs inhibit bradykinin-induced bronchoconstriction in patients with asthma,[44] with nedocromil being more potent, as it is in most anti-inflammatory effects. Inhibitory effects on the upregulation of ICAM-1 have been shown for both for sodium cromoglycate[45] and nedocromil.[46] Furthermore, the ability of both drugs to inhibit TNFα production,[47] and the reduction by nedocromil of the effects of IL-1β,[48,49] would be expected to contribute to inhibitory effects on ICAM-1 *in vivo*. Inhibition of the potent neutrophil chemotactic agent IL-8 has also been shown for nedocromil sodium.[49,50] However, even if the production of IL-8 correlates with rhinovirus replication *in vitro*,[9] the clinical relevance remains uncertain.

Nedocromil has been used in a double-blind placebo-controlled inoculation study.[1] Healthy volunteers were treated for 7 days with nasal drops containing nedocromil 1.3mg or matching placebo in each nostril 4 times daily. Rhinovirus (39 patients), coronavirus (53 patients) or saline (10 patients) were given as nasal drops after the fifth dose of nedocromil. In the rhinovirus trial, daily symptom scores and nasal secretion weights were significantly lower in the group treated with nedocromil. In the coronavirus trial there were insignificant trends in favour of nedocromil. In both trials the impairment of performance in volunteers who developed a cold was significantly less in those treated with nedocromil than in those treated with placebo. The drug was well tolerated. The conclusions were that common inflammatory mediators can be postulated in allergic disorders and the common cold.

Sodium cromoglycate has been used in a double-blind placebo-controlled study of 135 patients.[51] Adult patients who attended employee health clinics with the symptoms of acute cold for less than 24 hours were treated with intranasal sodium cromoglycate 5.2mg per nostril and inhaled sodium cromoglycate 20mg every second hour during daytime for 2 days, and 4 times daily for the following 5 days. Patients with chronic respiratory diseases, with particular attention to asthma and allergic rhinitis, were excluded. Statistical analyses of the 118 patients who met the eligibility criteria and com-

pleted registration of symptom scoring at home showed a significant reduction of the sum of general symptoms (general malaise, body aches and pains and attacks of chill and shivering) and upper and lower respiratory symptoms (sneezing, nasal running, nasal blockage, sore throat, cough and disturbance of voice). Most individual symptoms resolved significantly faster in the sodium cromoglycate group than in the placebo group, and the patients' opinion of efficacy favoured sodium cromoglycate significantly.

These 2 studies give indications of effects that should be further confirmed and explored. Particularly for sodium cromoglycate, the long record of safety should warrant general use in a frequent but not particularly serious condition like the common cold. The fact that useful efficacy has been shown when treatment was started after the onset of symptoms makes the drug more suitable for general use in URTIs than if prophylactic administration were necessary. Considering the possible effect of URTIs on the incidence and severity of asthma and allergic diseases,[52,53] another property of sodium cromoglycate, its ability to inhibit the switch to IgE synthesis and secretion in human B cells,[54] may be of importance in this context. A combined antiasthmatic and anti-infective effect is of particular interest for the position of the drugs in asthma treatment, and is an important subject for further studies.

2.3 Corticosteroids

The corticosteroids are a mainstay in the treatment of asthma and allergic disorders. They have the most potent anti-inflammatory effect of all clinically used drugs,[55] exerting inhibiting effects *in vitro* on all cytokines and cellular systems involved in asthma as well as in respiratory infections. The drugs reduce plasma exudation in human airways, probably more due to inhibition of cellular mechanisms than a direct vascular antipermeability effect.[56]

In 1 trial, prophylactic treatment with beclomethasone 168μg intranasally twice a day from 4 days before intranasal challenge with rhinovirus until 5 days after challenge was combined with oral prednisolone 30mg for 3 days, beginning 1 day before challenge.[7] The study comprised 44 patients, of whom all shed virus during the study, with a tendency to longer shedding of virus and lower rate of seroconversion in the corticosteroid group. During the prednisolone treatment, for the first 2 days after challenge, nasal obstruction, nasal mucus weights and kinin concentrations in nasal lavages were lower in the corticosteroid recipients. An increase in IL-1β in nasal lavage in the symptomatic patients was not inhibited by the treatment.[8] Subsequent increases in these variables in the corticosteroid group, however, resulted in no significant cumulative changes between treatment groups.

The study above illustrates the discrepancy between *in vitro* and *in vivo* effects. A strong inhibition of IL-1 is seen *in vitro*,[55] and absence of such an effect paralleled the absence of effects on symptoms in the study above.[8] Still, many of the anti-inflammatory effects of the corticosteroids could be beneficial in viral respiratory infections. However, the potential adverse effects of these drugs probably outweigh any benefits.

The immunosuppressive effect of the corticosteroids is utilised in transplantation medicine and autoimmune disorders, where a major adverse effect of high dose corticosteroids is increased risk of infections.[57] Increased risks of infections, however, are also observed even with physiological levels of corticosteroids stimulated under stress[58] and in treatment of skin disorders with topical corticosteroids.[59] Case reports exist of fatal herpes virus infection after corticosteroid use for upper airway obstruction in mononucleosis,[60] and of severe varicellae after intranasal corticosteroids for chronic sinusitis.[61] In a safety study of a new inhaled corticosteroid for asthma treatment, increased URTIs were considered to be related to the treatment.[62] It is possible that even subtle immunosuppressive effects of topical corticosteroids may neutralise any beneficial inhibitory effects on airway inflammation in viral respiratory infections, possibly even with a risk for negative balance. Other adverse effects, for children mainly the impact on

growth, underline the inappropriateness of corticosteroid treatment for URTIs. Intranasal corticosteroids for allergic rhinitis cause a significant reduction of lower leg growth in children after treatment for 6 weeks,[63] a not unreasonably long annual time for colds in children.[64]

2.4 β_2-Agonists

The β_2-agonists are potent inhibitors of mediator release from human lung cells *in vitro*.[65-67] Their antiasthmatic effect is mainly considered to be an effect on smooth muscles, but even in the nose, where there is no smooth muscle, β_2-agonists reduce the increase in nasal resistance in response to allergen to some extent.[68] Another possible mechanism of action is the stimulation of mucociliary clearance that has been reported from some studies[69,70] but not from others.[71,72] Such an effect may be of particular relevance in URTIs in patients with other underlying airway disease that could make them more susceptible to bacterial complications in the lower airways. The β-agonists are able to inhibit cholinergic neurotransmission in animals[73] and in human bronchi.[74] Theoretically, the cholinergic upregulation and enhanced 'functional β-blockade' in viral infections would be counteracted by exogenously administered β-agonists.

In a study in healthy individuals, salbutamol (albuterol) did not inhibit the cough reflex in response to capsaicin challenge.[75] In another study of cough induced by substance P in patients with colds, the cough was completely inhibited by treatment with procaterol 50μg orally.[76] In a study of patients with acute bronchitis, i.e. productive cough for less than 30 days, inhalation of salbutamol reduced the number of patients coughing after 7 days, independently of cigarette smoking and use of erythromycin.[77] No clinical trial has been published of β-agonist treatment of URTIs in nonasthmatic patients. Placebo-controlled studies of salbutamol treatment in pertussis have failed to prove any effect.[78,79]

2.5 Anticholinergics

The basic cholinergic tone is increased in asthma[80] and chronic obstructive pulmonary disease,[81] which provides a practical reason for using anticholinergics in these conditions. Airway secretion from mucous and seromucous glands plays an important role in the production of rhinorrhoea in URTIs, and is mainly stimulated by cholinergic activity.[82] Natural anticholinergic drugs are the oldest pharmacological treatment of bronchial asthma, but carry substantial adverse effects. The compounds inhibit muscarinic receptors which are widespread in the body; the development over the last decades of synthetic quaternary compounds with limited resorption from the airway mucosa has made it possible to minimise the adverse effects to other organs.

Atropine methonitrate had no effect on symptoms in experimental rhinovirus infection at a dosage of 125μg in each nostril 3 times daily, but reduced nasal mucus production at a dosage of 250μg 4 times daily.[83] Nasal bleeding was observed in 33% of infected patients and in 20% of noninfected volunteers.

The topical anticholinergic ipratropium bromide reduced nasal discharge in 2 studies of experimental rhinovirus infection at a dosage of 80μg instilled in each nostril 3 times a day, beginning 24 hours after the first virus challenge.[84,85] The number of patients developing clinical infection in terms of shedding virus was reduced,[84] as well as the number of patients shedding virus after 5 days of treatment.[85] The treatment was generally well tolerated.

Ipratropium bromide has also been used in 2 studies of naturally acquired cold,[86,87] both studies showing significant reduction of nasal secretions during the first days of treatment. The larger study[87] was of 317 patients who used ipratropium bromide 84μg in each nostril 4 times a day, beginning within 36 hours after the onset of symptoms. The reduction of nasal discharge was most pronounced in patients with more severe rhinorrhoea, an average of 23%. The findings were consistent between patients' subjective assessments of severity and the weight of nasal discharge.

In conclusion, ipratropium bromide has been shown to give a slight to moderate reduction of

nasal discharge with few adverse effects when administered intranasally. However, no other symptoms such as sneezing or nasal congestion were reduced. A study combining ipratropium bromide with nasal interferon-α-2b and oral naproxen in the treatment of experimental rhinovirus infection showed a tendency to a reduction of all symptoms as well as a significant reduction of days of virus shedding.[88] Considering the narrow scope of effects of the drug alone, combination with other drugs appears indicated in clinical use of ipratropium bromide against URTIs.

2.6 Xanthines

The main effect of this group of asthma drugs is smooth muscle relaxation due to inhibition of cyclic AMP phosphodiesterase.[89,90] Theophylline has been shown to increase mucociliary transport,[91,92] inhibit histamine release[93] and 'late reactions'[94] after allergen challenge tests, and to decrease permeability oedema induced by different inflammatory mediators.[95] However, the clinical relevance of these anti-inflammatory effects has not been evaluated in asthma or in respiratory infections.

3. Conclusions

The wide variety of viruses causing URTIs[96] and the difficulties in making a specific diagnosis at onset of symptoms make it less likely that antiviral drugs against URTIs will be available for general use in the foreseeable future. The groups of drugs discussed in this paper interfere with pathogenetic pathways in viral respiratory infections, and inhibitory effects on symptoms have been obtained with oral antihistamines and with topically active anticholinergics and chromones.

A treatment for URTIs should firstly be without adverse effects and should also preferably involve the possibility of adjusting dosages to the varying severity of the infections, i.e. have a wide and safe therapeutic range. From this aspect, the chromones, and particularly sodium cromoglycate with its long record of safety, may be of particular interest. Further exploration of effects and development of treatment regimens, possible combination of drugs and optimising administration of local treatments may lead to substantial progress in this field, which despite its magnitude is still short of effective treatment alternatives.

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