Clinical and Experimental Allergy, 1996, Volume 26, pages 989–994

EDITORIAL

Cromolyns: treatment for the common cold?

As I sit writing this editorial only 2 weeks into the New Year, I can report that I have already suffered two upper respiratory tract viral infections or 'common colds'. The first was a particularly nasty affair with symptoms representing almost a full house of those commonly recognized in this syndrome. Namely, sore throat, tracheitis, severe cough, to be followed swiftly by a runny nose and severe nasal blockage which inevitably lead to sinusitis associated with severe headache. The final insult was the development of a severe and highly productive bronchitis! As if this were not enough, just as I was beginning to recover a second virus assaulted me and turned my nose into a swiftly running tap for 36 h, though thankfully this virus was considerate enough to leave it at that. It is possible that these were a punishment for over-indulgence in the revelries associated with the holiday season, but it is also possible that they were sent as a timely reminder that I should get on with this editorial which I had been 'thinking about' but not actually doing, for a few weeks! They also served to remind me that the search for the cure of the common cold or indeed a reasonably effective treatment thereof has been a focus of intensive research for 40–50 yr, so far without very encouraging results. A further study is reported in the pages of this journal showing that an established asthma treatment is also effective in the treatment of the common cold [1]. I will consider the implications of these findings later in this article, but first I will consider the epidemiology and mechanisms of the common cold and briefly review previous studies [1].

Epidemiology of the common cold

The common cold is probably the most frequent illness afflicting mankind, and is certainly the number one cause of consultations with primary care medical practitioners. It is also associated with a great deal of industrial and school absenteeism. Based on current estimates, adults are thought to have an average of five illnesses per annum, with school age children following at around 8-12, and infants probably suffering even more frequent afflictions. There are numerous factors influencing the epidemiology of viral upper respiratory tract infections, including individual and community immunity, seasonal variation, socioeconomic factors such as nutrition and population density, and perhaps most important of all, family structure. It is well known that pre-school and school age children are the most frequent introducers of new viruses into families. The influence of socioeconomic factors is highlighted by a study in Brazil where almost continuous infection was detected in a densely-crowded, urban, economically-deprived setting. The epidemiology of viral respiratory tract infections has been considered in much more detail elsewhere [2].

It is thought that there are well over 200 individual viruses or atypical bacteria associated with the common cold, but these can be grouped into eight or nine virus types. Rhinoviruses, of which there are over 100 serotypes are the most common cause of the common cold, accounting for 50–60%. The next most common are coronaviruses, of which there are two main serotypes infecting humans; they are thought to cause around 15% of common colds. Respiratory syncytial (RS) virus, influenza viruses A, B and C, and parainfluenza viruses 1–4 are the next most common, but their incidence is very much dependent on factors such as age and immunity. Other viruses associated with the common cold include adenoviruses and enteroviruses and both *Mycoplasma* and *Chlamydia pneumoniae* have also been associated.

Complications of the common cold

In addition to the common cold, upper respiratory viral infections are associated with more severe disease, particularly in the presence of significant disease elsewhere, for example chronic respiratory or cardiac disease. Virus infections have been associated with as many as 85% of exacerbations of asthma in children [3] and 40–60% of exacerbations in adults [4]. RS virus is the major cause of bronchiolitis and as such is associated with enormous morbidity and mortality, and influenza virus has been associated with enormous mortality in the major epidemics throughout the last century, most notably that of 1918 which reportedly was responsible for more deaths than the First World War.

Mechanisms of virus-induced inflammation

The symptoms of the common cold principally involve rhinorrhoea, a result of a combination of vascular leakage and mucous secretion, and nasal blockage, chiefly a result of mucosal oedema, consequent upon vascular engorgement and inflammatory infiltration.

Inflammatory mediators

Several studies have looked for inflammatory mediators

in upper respiratory tract infections, with the most convincing evidence so far being in favour of kinins [5]. Several studies have looked for other mediators of acute inflammation, including histamine and prostaglandin D_2, without success [5,6]. This is somewhat surprising as numerous studies have demonstrated increased basophil histamine release on incubation with a variety of respiratory viruses [7] and this has recently been confirmed in wild type infections *in vivo* [8]. Recent studies have confirmed raised levels of histamine in nasal secretions both in experimental colds [9] and in wild type infections [10]. Both these studies have found raised levels of histamine but only amongst atopic subjects. Leukotriene C_4 has been detected in nasal pharyngeal secretions in 33% of infants with upper respiratory tract infection [11] and we have recently demonstrated increased basophil leukotriene C_4 production in adults with wild type symptomatic colds [12].

Inflammatory cell infiltration

Neutrophil infiltration has long been recognized as an important factor in upper respiratory tract infections [13,14]. This has recently been confirmed in nasal secretions in several studies, though a recent study examining nasal biopsies [15] failed to demonstrate a neutrophil infiltrate in the nasal mucosa. This is probably explained by the fact that neutrophils may only be resident in the nasal mucosa transiently, as they pass from the blood stream into the nasal lumen. A further recent study in wild type colds [16] has demonstrated increased neutrophil myeloperoxidase, suggesting that these cells are also activated to release their toxic products. A peripheral blood leucopenia has been demonstrated many times in the presence of viral infections and Levandowski demonstrated increased numbers of lymphocytes in nasal secretions using flow cytometry [13]. Interestingly we have recently demonstrated a $CD3^+$, $CD4^+$ and $CD8^+$ lymphocyte infiltration in the bronchial mucosa of normal subjects undergoing experimental rhinovirus infection [17]. Eosinophil and eosinophil products such as eosinophil catonic protein and major basic protein, have also been implicated in virus-associated wheezing episodes [18,19], and we have also demonstrated a bronchial eosinophilia during experimental colds in both normal and asthmatic subjects [17].

Cytokine production

Interferon (IFN) has long been recognized as an important product of viral respiratory tract infection, but more recent studies have implicated a number of other cytokines. Interleukin (IL)-8 is most prominent amongst these and has recently been associated with neutrophil influx in common colds [16]. Other cytokines that have been found in nasal secretions in the presence of symptomatic colds include TNFα, IL-6, IFN-γ, IL-1β [10], IL-11 [20], RANTES and MIP 1α [21], IFN-α [23] and in a number of cases of virus-associated wheeze small amounts of IL-5 but not IL-4 [23].

Nitric oxide

Nitric oxide is thought to have pro-inflammatory effects in the airways and has recently been found in increased levels in subjects with symptomatic upper respiratory tract infection [24]. Inducible nitric oxide synthase expression is increased in asthma and is inhibited by glucocorticoid therapy.

Therapies for the common cold

Many therapies for the common cold have been tried over the last 2000 years, though none so far has been successful. One that has gained some popularity with the public has been the taking of large doses of vitamin C. There have been a large number of studies in both experimental infections and wild type infections with very varying results. There have also been contrasting review articles: one in 1975 concluded that there was no effect, while another using much the same data, more recently, claims that vitamin C can reduce the duration of illness by an average of 1 day (approximately 20%) [25]. Another interesting treatment that has been tried recently is the inhalation of humidified hot air at 43°C which has been shown to reduce the severity of symptoms [26].

Interferons

Nasal IFNα has perhaps been the most successful treatment employed, having been first studied over 20 years ago. It is undoubtedly effective when given shortly before or after exposure to the virus and also when given prophylactically to contacts in family outbreaks [27,28]. However, it has not gained favour with the general population or with pharmaceutical companies, owing to a number of drawbacks such as the expense of production, the frequency of dosage and also problems with local bleeding and discharge with long-term use.

Virus antagonists and inhibitors of virus uncoating

A large number of compounds have been studied that inhibit viral infection by preventing virus uncoating or virus entry into the cell, or various stages in virus

replication once the virus has gained entry to the cell. There are too many such studies to mention them individually here, but suffice it to say that no effective drug has emerged so far because of a combination of factors, including drug toxicity and the very rapid emergence of resistant viruses resulting from the rapid mutation rate that viruses are known to possess. More recently, following the identification of several cell surface proteins that act as virus receptors and are involved in virus entry into the cell, efforts have been targeted at blocking virus receptor binding. One particular focus of attention has been rhinovirus and its binding to ICAM-1 which is the receptor for 90% of rhinoviruses. This has been reviewed recently [29], and trials with monoclonal antibodies and with soluble ICAM-1 have been encouraging both *in vitro* and in animal studies. It is too soon to say yet whether these drugs will be effective, and whether they will be amenable to large scale production and have sufficiently long residence times in the nasal cavity to be clinically useful. Another note of caution is on the emergence of resistant strains. It had been thought that any mutations producing resistance would result in non-viability, as receptor binding is an essential step to virus replication. However, there is an initial report of emergence of a strain of polio virus, resistant to neutralization by soluble receptor [30].

Vaccines

Vaccine development has been a priority in medical research for many years, as it has long been thought the most effective way of controlling virus-induced disease. There are many precedents of successful vaccination programmes, including smallpox and polio. Vaccine programmes for respiratory viruses have been much less successful, however. Influenza vaccine is relatively effective despite the marked antigenic shift and drift, though at the cost of great expense, resulting from the intensive vigilance needed to keep up with the viruses' effort at evasion.

RS virus has been the next target for vaccine production but received a major setback when formalin inactivated vaccines were found to be associated with eosinophilic pneumonitis and increased morbidity and mortality on subsequent natural exposure to the virus. These adverse results have set back RS virus vaccine development by at least 20 yr and have meant that current efforts need to proceed with extreme caution. Considerable research has been undertaken to determine why such adverse effects resulted from this vaccine and present thoughts suggest that different RS virus surface proteins are capable of inducing very different cellular immune responses. The F protein and 22K produce a Th-1 type and cytotoxic response, while the G protein favours a Th-2 type response [31]. Clinical studies with F subunit vaccines are now underway and it is hoped that an effective vaccine may not be too far in coming. There are also initial trials with parainfluenza type 3 vaccines, but the other respiratory viruses have commanded relatively little attention. Rhinovirus in particular has been a very difficult target for vaccine design, as there are well over 100 different serotypes, which are serotype specific in their induction of neutralizing antibody responses. Recent work, however, has suggested that T cell responses are relatively conserved across serotypes and this may be a fruitful area for future research.

Corticosteroids and over the counter medicines

Corticosteroids are known to have widespread anti-inflammatory effects, including reducing inflammatory cell infiltration and cytokine production. Corticosteroids have been assessed in randomized controlled trials and have been shown to reduce inflammation and symptoms during the first 2 days; however, there appeared to be rebound effect when treatment was stopped, and there were no significant differences overall [32].

The use of high dose inhaled oral steroids for the common cold is therefore not justified, particularly in view of the known side-effects. Steroids, however, may have a very much more effective and more logical place in the treatment of virus-associated wheezing illness. There have been several recent studies of inhaled steroids in virus-associated wheeze in children of varying ages. One of the earlier studies used high dose inhaled beclomethasone (750 μg tds for 5 days), at the first sign of acute asthma in pre-school children. There was a clear reduction in both day-time and night-time symptoms and a blind preference for active treatment [33]. These results have been confirmed in a more recent study [34]. Another recent study in infants using 400 μg of inhaled beclomethasone daily, failed to show any improvement in lung function or symptoms in recurrently wheezy infants, though there may have been a beneficial effect on bronchial hyperresponsiveness [35]. These three studies have all used intermittent high dose inhaled steroids.

Two very recent studies have examined the effect of continuous lower dose inhaled steroids on episodic viral-induced wheezing episodes. Both studies used 400 μg inhaled steroid per day, the first in pre-school children [36], and a second in 7–9-year-old children [38]. The treatment periods were 4 months and 7 months respectively and in neither study was there any benefit in terms of lower respiratory symptom episodes. These studies demonstrate that low dose inhaled steroid is ineffective against virus-induced wheezing attacks, and that high

dose therapy is only partially effective. There is a clear need for further studies of different dosages and different age groups, and also for the development of alternative therapy, as at this stage it seems unlikely that steroids will provide any more than a partial benefit.

Mediator antagonists

Several studies have failed to demonstrate elevated histamine levels in association with the common cold [6,38]. Smith and Remigio [39] demonstrated elevated histamine concentrations in nasal secretions of children with respiratory virus infection and these findings have recently been confirmed though only in atopic subjects [9,10]. Two studies of antihistamines in the common cold showed beneficial effects in terms of symptomatology when treatment was started 24–48 h after symptom onset; however, the magnitude of effects was relatively small [40,41]. A more recent study comparing orally administered chlorpheniramine and local diphenhydramine found no significant benefit [42]. Since these studies were carried out several more potent non-sedating antihistamines have been introduced and interestingly one of these appears to reduce epithelial cell ICAM-1 expression [43]. This property is of particular interest in view of the known role of ICAM-1 in inflammation, and its role as the cellular receptor for major group rhinoviruses. It would now seem timely to reassess the role of more potent antihistamines, particularly in virus-induced wheezing episodes.

Elevated levels of kinins have been found in association with experimental colds [6]; however, only one trial a of bradykinin antagonists has been carried out, unfortunately with negative results [44]. Further studies with more potent bradykinin antagonists are awaited.

Combination therapies

Over the counter medicines have long been used for symptomatic relief during colds, with benefits being ascribed chiefly to their antipyretic effects, though anti-inflammatory effects may also be involved. Several studies have examined the effects of non-steroidal anti-inflammatory agents and anti-cholinergic agents with variable results.

Recently Gwaltney proposed that a combined antiviral and anti-inflammatory effect would be required for effective suppression of symptoms, as neither agent appeared very effective on its own. He therefore carried out a blinded placebo controlled study, comparing intranasal IFNα combined with intranasal ipratropium and oral naproxen begun 24 hours after experimental rhinovirus infection; treatment was continued three times daily for 4 days. Antiviral effect was demonstrated, in that virus shedding was significantly reduced and the mean virus titre was also reduced. The number of clinical colds, the mean symptom score, mucus secretion, cough and general malaise were all significantly reduced in treated subjects and medications were well tolerated [45]. Interestingly, the symptom that was least effectively treated in this study was sneezing, and it may be that the addition of an antihistamine to the cocktail tested above would be more effective.

Use of cromolyns for the treatment of the common cold

An earlier study with nedocromil sodium and placebo control in experimental colds showed a reduction in symptoms associated with an improvement in performance impairment [46]. This study employed intranasal nedocromil alone and it may be that combined intranasal and inhaled therapy may be more effective. These were the methods chosen by the authors of the report in this issue [1], who carried out a double blind placebo controlled study of intranasal and inhaled sodium cromoglycate in adults with symptoms of a common cold. This study was carefully conducted and went to great lengths to exclude subjects with a history of allergic rhinitis. Subjects had symptoms of a cold for less than 24 h prior to entry in the study and were treated with cromoglycate for 7 days with 20 mg inhaled and 5.2 mg per nostril intranasally, 2-hourly for days 1 and 2, and 4 times daily for days 3–7. Symptoms were recorded on a diary card and active treatment was found to be associated with swifter resolution of symptoms and reduced severity of symptoms in the last 3 days of treatment. The treatment was very well tolerated, with no significant side-effects. These studies are encouraging in that they were carried out after symptoms had begun and still demonstrated a significant reduction in symptoms in adults with common colds.

Use of cromolyns for virus-induced asthma exacerbations

In addition to the above studies on the common cold there is also some recent evidence that cromolyns can be of use in the treatment of virus-induced asthma exacerbations. Konig *et al.* [47] have recently published a study comparing nedocromil sodium as a prophylactic medication during the Winter season, when viral respiratory infections are most common. This study was placebo controlled and involved taking nebulized nedocromil sodium 0.5% three times daily for 24 weeks during the Winter season. Ninety-three children aged 6–12 years took part and completed the study with no serious adverse events. Nedocromil was associated with a

decrease in the number of symptomatic days over the whole treatment period and with decreases in mean asthma scores, in cough, in beta 2-agonist rescue therapy, and with an increase in mean peak flow of 10 L per min (5% of baseline peak flow). The authors also examined periods of symptomatic respiratory infections specifically, and found that nedocromil sodium was accompanied by a more rapid resolution of asthma symptoms immediately following presumed infections.

Conclusion

The common cold viruses that we presently know about have all been discovered between the 1930s and the 1960s and have stimulated a great deal of research aimed at finding an effective treatment. Success has so far evaded research and development companies, with the relative exception of the influenza vaccine. One of the major barriers to development of an effective treatment is that viral replication seems to be at its peak just prior to or on the day of the first occurrence of symptoms. There is therefore a very small window of opportunity for introducing an effective treatment. The fact that the authors of the present study [1] were able to demonstrate an effect after symptoms had begun is very encouraging and suggests that further research into this class of compounds is indicated. The possible mechanisms of action are intriguing and though there is a good deal of information available on the mechanisms of action of cromolyns in asthma, there is very little information on the effect of these compounds in virus infection. One report suggests an effect on cytopathic effect at very high concentrations, but no direct effect on viral replication [48], and these findings were confirmed in a subsequent study [49].

In view of the discouraging results obtained with inhaled steroids in virus-induced wheeze in children, the known anti-inflammatory effects of cromolyns in asthma, and the finding that cromolyns are also helpful in the common cold and in the single study of virus-induced wheeze in children carried out, further studies to examine the efficacy of inhaled and intranasal cromolyns in virus-induced wheeze in both children and adults would seem timely, as would further work to investigate the possible mechanisms of action.

References

1 Aberg N, Aberg B, Alestig K. The effect of inhaled and intranasal sodium cromoglycate on symptoms of upper respiratory tract infections. Clin Exp Allergy 1996 (in press).

2 Johnston SL, Holgate ST. Epidemiology of viral respiratory tract infections. In: Myint S, Taylor-Robinson D, eds. Viral and other infections of the human respiratory tract. London: Chapman & Hall, 1996: p 1–38.

3 Johnston SL, Pattemore PK, Sanderson S et al. Community study of role of viral infections in exacerbations of asthma in 9–11 year old children. Br Med J 1995; 310:1225–8.

4 Nicholson KG, Kent J, Ireland DC. Respiratory viruses and exacerbations of asthma in adults. Br Med J 1993; 307:982–6.

5 Naclerio RM, Proud D, Lichtenstein LM et al. Kinins are generated in experimental rhinovirus colds. J Infect Dis 1988; 157:133–45.

6 Naclerio RM, Proud D, Kagey-Sobotka A et al. Is histamine responsible for the symptoms of rhinovirus colds? A look at the inflammatory mediators following infection. Paediatr Infect Dis J 1988; 7:219–22.

7 Bardin PG, Johnston SL, Pattemore PK. Viruses as precipitants of asthma symptoms II. Physiology and mechanisms. Clin Exp Allergy 1992; 22:809–22.

8 Thomas LH, Corne JM, Johnston SL et al. Integrin clustering causes increased histamine release (HR) from basophils of patients with symptomatic colds. FASEB J 1995; 9:A1046.

9 Igarashi Y, Skoner DP, Doyle WJ et al. Analysis of nasal secretions during experimental rhinovirus upper respiratory infections. J Allergy Clin Immunol 1993; 92:722–31.

10 Lau LCK, Corne JM, Scott SJ et al. Nasal cytokines in common cold. Am J Respir Crit Care Med (abstract) 1996; 153;A697.

11 Volovitz B, Welliver RC, de Castro G et al. The release of leukotrienes in the respiratory tract during infection with respiratory syncytial virus: role in obstructive airway disease. Pediatr Res 1988; 24:504–7.

12 Thomas LH, Corne JM, Johnston SL et al. Changes in circulatory leukocyte responses during symptomatic colds. Proceedings of AAAI/ATS asthma meeting, Chicago, Illinois, July 1995. p. 23.

13 Levandowski RA, Weaver CW, Jackson GG. Nasal-secretion leukocyte populations determined by flow cytometry during acute rhinovirus infection. J Med Virol 1988; 25:423–32.

14 Winther B, Farr B, Turner RB. Histopathologic examination and enumeration of polymorphonuclear leukocytes in the nasal mucosa during experimental rhinovirus colds. Acta Otolaryngologica Supplement (Stockholm) 1984; 413:19–24.

15 Fraenkel DJ, Bardin PG, Sanderson G et al. Immunohistochemical analysis of nasal biopsies during rhinovirus experimental colds. Am J Respir Crit Care Med 1994; 10:1130–36.

16 Teran L, Johnston SL, Schröder J-M et al. Relationship of interleukin-8 to neutrophil influx in naturally occurring colds in asthmatic children. Am J Respir Crit Care Med 1996; submitted.

17 Fraenkel DJ, Bardin PG, Sanderson G et al. Lower airways inflammatory response during rhinovirus colds in normal and asthmatic subjects. Am J Respir Crit Care Med 1995; 151:879–86.

18 Seminario M-C, Squillace D, Bardin PG et al. Increased levels of eosinophil major basic protein in nasal secretions in rhinovirus infection. J Allergy Clin Immunol 1995; 95:259.
19 Heymann PW, Rakes GP, Hogan AD et al. Assessment of eosinophils viruses and IgE antibody in wheezing infants and children. Int Arch Allergy Immunol 1995; 107:380–2.
20 Einarsson O, Geba GP, Panuska JR et al. Asthma-associated viruses specifically induce lung stromal cells to produce interleukin-11, a mediator of airways hyperreactivity. Chest 1995; 107:132–3s.
21 Teran LM, Johnston SL, Holgate ST. Immunoreactive RANTES and MIP-1α are increased in the nasal aspirates of children with virus-associated asthma. Am J Respir Crit Care Med 1995; 151:A385.
22 Taylor CE, Webb MSC, Milner AD et al. Interferon alfa, infectious virus, and virus antigen secretion in respiratory syncytial virus infections of graded severity. Arch Dis Child 1989; 64:1656–60.
23 Johnston SL, unpublished observations.
24 Kharitonov SA, Yates D, Barnes PJ. Increased nitric oxide in inhaled air of normal human subjects with upper respiratory tract infections. Eur Respir J 1995; 8:295–7.
25 Hemilä H, Herman ZS. Vitamin C and the common cold: a retrospective analysis of Chalmers' review. J Am Coll Nutrition 1995; 14:116–23.
26 Tyrrell D, Barrow I, Arthur J. Local hyperthermia benefits natural and experimental common colds. Br Med J 1989; 298:1280–3
27 Sperber SJ, Hayden FG. Chemotherapy of rhinovirus colds. Antimicrobial Agents Chemother 1988; 32:409–19.
28 Douglas RM, Moore BW, Miles HB et al. Prophylactic efficacy of intranasal alpha2-interferon against rhinovirus infections in the family setting. N Engl J Med 1986; 314:65–70.
29 Johnston SL, Bardin PG, Pattemore PK. Viruses as precipitants of asthma symptoms III. Rhinoviruses: molecular biology and prospects for future intervention. Clin Exp Allergy 1993; 23:237–46.
30 Kaplan G, Peters D, Racaniello VR. Poliovirus mutants resistant to neutralization with soluble cell receptors. Science 1990; 250:1596–99.
31 Alwan WH, Kozlowska WJ, Openshaw PJM. Distinct types of lung disease caused by functional subsets of antiviral T cells. J Exp Med 1994; 179:81–9.
32 Farr B, Gwaltney JM Jnr, Hendley JO et al. A randomized controlled trial of glucocorticoid prophylaxis against experimental rhinovirus infection. J Infect Dis 1990; 162:1173–7.
33 Wilson NW, Silverman M. Treatment of acute, episodic asthma in preschool children using intermittent high dose inhaled steroids at home. Arch Dis Child 1990; 65:407–10.
34 Connett G, Lenney W. Prevention of viral induced asthma attacks using inhaled budesonide. Arch Dis Child 1993; 68:85–7.
35 Stick SM, Burton PR, Clough JB et al. The effects of inhaled beclomethasone dipropionate on lung function and histamine responsiveness in recurrently wheezy infants. Arch Dis Child 1995; 73:327–32.
36 Wilson N, Sloper K, Silverman M. Effect of continuous treatment with topical corticosteroid on episodic viral wheeze in preschool children. Arch Dis Child 1995; 72:317–20.
37 Doull IJM, Lampe F, Holgate ST. Effect of regular inhaled corticosteroids on episodes of viral associated wheezing in school age children. Proceedings of the British Paediatric Association 1996; in press.
38 Eggleston PA, Hendley JO, Gwaltney JM Jr. Mediators of immediate hypersensitivity in nasal secretions during natural colds and rhinovirus infection. Acta Otolaryngol (Stockh) 1984; 413 (Suppl.):25–35.
39 Smith TF, Remigio LK. Histamine in nasal secretions and serum may be elevated during viral respiratory tract infections. Int Arch Allergy Appl Immunol 1982; 67:380–3.
40 Crutcher JE, Kantner TR. The effectiveness of antihistamines in the common cold. Pharmacology 1981; 21:945–52.
41 Howard JC, Kantner TR, Lilienfield LS et al. Effectiveness of antihistamines in the symptomatic management of the common cold. JAMA 1979; 242:2414–7.
42 Gaffey MJ, Gwaltney JM Jnr, Sastre A. Intranasally and orally administered antihistamine treatment of experimental rhinovirus colds. Am Rev Respir Dis 1987; 136:556–60.
43 Vignola AM, Crampette L, Mondain M et al. Inhibitory activity of Loratidine and decarboxoithoxyloratidine on expression of ICAM-1 and HLA DR by nasal epithelial cells. Allergy 1995; 50:200–3.
44 Higgins PG, Barrow GI, Tyrrell DAJ et al. A study of the efficacy of the bradykinin antagonist NPC 567 in rhinovirus infections in human volunteers. Antiviral Res 1990; 14:339–44.
45 Gwaltney JM Jr. Combined antiviral and antimediator treatment of rhinovirus colds. J Infect Dis 1992; 166:776–782.
46 Barrow GI, Higgins PG, Al-Nakib W et al. The effect of intranasal nedocromil sodium on viral upper respiratory tract infection in human volunteers. Clin Exp Allergy 1990; 20:45–51.
47 Konig P, Eigen H, Ellis MH et al. The effect of nedocromil sodium on childhood asthma during the viral season. Am J Respir Crit Care Med 1995; 152:1879–86.
48 Penttinen K, Aarnio A, Hovi T. Disodium cromoglycate can inhibit virus-induced cytopathic effects in vitro. Br Med J 1977; 1:82.
49 Loveday DEE, Wenham RBM. Effect of disodium cromoglycate on virus-cell systems in vitro. Br Med J 1977; 2:557–8.

S. L. Johnston
University Medicine
D Level Centre Block
Southampton General Hospital
Southampton
UK SO16 6YD