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Review article

Supported by a grant from Zeneca Pharmaceuticals

Epidemiology, pathogenesis, and treatment of the common cold

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Objective: Reading this article will reinforce the reader's knowledge of the pathogenesis of the common cold. The rationale for current and potential therapies for the common cold are reviewed in the context of current concepts of the pathogenesis of these illnesses.

Data Sources and Study Selection: A MEDLINE literature search was done using the search terms common cold, rhinovirus, and viral respiratory infection. The search was restricted to the English language. Articles were selected for review if the title and/or abstract suggested the content was relevant to the subject of this review. The bibliographies of selected articles were used as a source of additional literature.

Results: Recent studies suggest that the host response to the virus is an important contributor to the pathogenesis of the common cold. Inflammatory mediators, especially the pro-inflammatory cytokines, appear to be an important component of this response and present an attractive target for new interventions for common cold therapies. Currently available treatments for the common cold have limited efficacy against specific symptoms. These therapies should be selected to treat the specific symptoms that are perceived to be the most bothersome by the patient.

Ann Allergy Asthma Immunol 1997;78:531–40.

INTRODUCTION

Viral upper respiratory infections account for approximately 50% of all illnesses and approximately 75% of illnesses in young infants.[1,2] Although these illnesses are generally mild and self-limited, they are associated with an enormous economic burden both in lost productivity and in expenditures for treatment. The common cold results in approximately 26 million days of school absence and 23 million days of work absence in the United States annually.[3] Each year we make approximately 27 million physician visits and purchase almost $2 billion worth of over-the-counter (OTC) cough and cold medications for treatment of common cold symptoms.[4] A recent survey of a representative sample of children 27 to 48 months of age found that 35% of children had received an OTC cold remedy in the preceding 30 days.[5]

EPIDEMIOLOGY

The pathogens most frequently associated with common cold symptoms are the rhinoviruses. Other important pathogens include the coronaviruses and respiratory syncytial virus (RSV). Influenza, parainfluenza, and adenoviruses may cause cold symptoms; however, these agents frequently cause lower respiratory or systemic symptoms in addition to the nasal symptoms characteristic of the common cold.[6] Colds occur year-round but have a decreased incidence during the summer months.[2,6,7] The "respiratory virus season" usually begins with an increase in incidence of rhinovirus infections in August or September and ends following the spring peak of rhinovirus infections in April or May. This period of increased incidence of disease is caused by sequential and relatively discreet outbreaks of different viral pathogens.[6,7] An increased incidence of common cold symptoms is associated with each of these outbreaks; however, other clinical syndromes are usually also present in the community during epidemics caused by pathogens other than rhinovirus or coronavirus.

The onset of common cold symptoms typically occurs one to two days after viral infection and the time to peak symptoms is generally two to four days.[8] The onset of illness and the time to peak symptoms is about one day later for the coronaviruses than for rhinoviruses or respiratory syncytial virus. A recent study suggests that subjects infected with rhinovirus may be able to detect the onset of symptoms as early as 16 hours after virus challenge.[9] Nasal obstruction, rhinorrhea, and sneezing are present early in the course of the cold; however, sore or "scratchy" throat is frequently reported as the most bothersome symptom on the first day of illness.[8,10,11] The sore throat resolves quickly and by the second and third day of illness the nasal symptoms are predominant. Cough is associated with approximately 30% of colds and typically does not become the most bothersome symptom until the 4th or 5th day of illness when the nasal symptoms decrease in severity.[8,10] The usual cold lasts about a week, although 25% last 2 weeks.[10] Virus shedding persists after the reso-

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Received for publication March 7, 1997.

Accepted for publication in revised form April 8, 1997.

lution of symptoms and virus may be cultured from 10% to 20% of subjects for 2 to 3 weeks after infection.[12,13]

The average incidence of the common cold in preschool children is 5 to 7 per year but 10% to 15% of children will have at least 12 infections per year.[1,14,15] The incidence of illness decreases with age and averages 2 to 3 per year by adulthood. The incidence of common colds in young children is affected by conditions that increase exposure such as other children in the home or extensive contact with children outside the home, as in childcare centers.[16–18] The difference in the incidence of illness between these groups of children decreases as the length of time spent in daycare increases; however, the incidence of illness remains higher in the daycare group through at least the first 3 years of life.[17]

Although the frequency of common colds suggests that person-to-person spread must be fairly efficient, natural transmission of rhinovirus appears to be surprisingly inefficient. A transmission rate of 38% was reported in a study in which one partner of a married couple was infected with rhinovirus and then the spouse, documented to be susceptible to the virus, was observed for acquisition of infection.[19] In another study, exposure of susceptible recipients to experimentally infected donors resulted in an infection rate of 44% in the recipients after 150 donor-hours of exposure.[20] Virus transmission rates are less than 10% following brief (3 to 36 hr) exposure to virus-infected subjects.[21]

There are three general mechanisms by which common cold viruses might be spread: (1) small-particle aerosols, (2) large-particle aerosols, and (3) direct contact. Although the various common cold viruses may presumably be spread by any of these mechanisms, some routes of transmission may be more efficient than others for particular viruses. Studies of experimental rhinovirus colds in human volunteers suggest that direct contact is the most efficient mechanism of transmission of this virus, although transmission by large particle aerosols has also been documented.[22,23] A study of natural colds found that treatment of the hands with a virucidal compound significantly reduced transmission of colds.[24] There were no rhinovirus infections in the subjects using the virucidal hand treatment in this study, a finding that supports the hypothesis that hand-to-hand transmission may be important in a natural setting. The transmission of the other pathogens associated with colds is less well studied. Respiratory syncytial virus appears to require close contact for spread and, in the experimental setting, has been spread by direct contact with contaminated fomites.[25] In contrast to rhinovirus and RSV, influenza appears to spread from person-to-person by small particle aerosol.[26,27]

Regardless of the route of transmission, studies of rhinovirus infection indicate that contact between the virus and the nasal mucosa appears to be important for initiation of infection. A very small inoculum of virus applied to the nasal cavity consistently results in infection in contrast to inoculation of virus into the oral cavity. The inoculum required for a 50% infection rate is calculated to be 0.3 tissue culture infectious dose 50 by the nasal route and 2260 tissue culture infectious dose 50 by the oral route.[21,28,29] Conjunctival inoculation of virus is also an efficient mechanism for initiation of rhinovirus infection, presumably because virus reaches the nasal cavity via the nasolacrimal duct.[13,29]

PATHOGENESIS

Much of the information relevant to the pathogenesis of the common cold is derived from studies in subjects experimentally infected with rhinovirus. The site of infection during rhinovirus infection is generally limited to the mucosa of the upper respiratory tract. Some of the pathogens associated with common cold syndromes (eg, parainfluenza viruses, RSV, and influenza) may produce different clinical syndromes by infecting the lower respiratory tract. Following inoculation into the nasal cavity, rhinovirus is first detected by cultures of the posterior nasopharynx.[13] As the cold progresses, virus is detected at more anterior sites in one or both nares.[13,30] Biopsies of the nasal mucosa and nasopharynx during experimental colds reveal focal infection that involves relatively few cells.[31] Ciliated epithelial cells are the primary cell involved although nonciliated cells are also infected. The apparent paucity of rhinovirus-infected cells may be a result of desquamation of infected cells into the nasal secretions.[32] Abnormalities of the paranasal sinuses may frequently be detected by computerized tomography or magnetic resonance imaging during both natural colds and experimentally-induced rhinovirus colds; however, studies to isolate virus from the sinuses during uncomplicated colds have not been done.[33,34] Although rhinovirus has been isolated from the lower respiratory tract of experimentally infected volunteers by bronchoscopy, it is difficult to exclude the possibility of contamination from the upper respiratory tract.[35,36]

The prominent symptoms of the common cold are rhinorrhea and nasal obstruction. Increased vascular permeability with leakage of serum into the nasal mucosa and nasal secretions is a major contributor to these symptoms.[37,38] The contribution of glandular secretions from the nose to the rhinorrhea becomes more important later in the course of the illness.[38] The mechanisms by which rhinovirus infection of the nasal epithelium results in increased vascular permeability and increased glandular secretions is not clear. Specimens of nasal secretions from human volunteers infected with rhinovirus contain small numbers of rhinovirus infected and uninfected ciliated epithelial cells, however, examination of specimens of the nasal epithelium by light or electron microscopy reveals no consistent lesions.[32,39,40] Similarly, no morphologic changes were seen in monolayers of human nasal epithelium infected with rhinovirus.[41] The absence of detectable histopathology during rhinovirus infection led to the suggestion that the host response to the virus may play a

primary role in the production of common cold symptoms.

Early studies of the host response to rhinovirus infection concentrated on the humoral immune response. Viral neutralizing activity, apparently associated with IgA, first appears in nasal secretions two to three weeks after infection at about the same time that neutralizing activity is detected in serum.[28,42–44] This neutralizing antibody in serum or nasal secretions is associated with serotype-specific protection from rhinovirus infection.[28,43,45] A recent study reported non-neutralizing rhinovirus-specific IgG and IgA in nasal secretions by the third day of rhinovirus illness.[46]

There is evidence that the cellular immune response may play a role in rhinovirus pathogenesis. The peripheral white blood cell count increases in infected, ill subjects during the first two to three days after virus challenge.[47] This increase in the WBC count is the result of an increase in the concentration of neutrophils. Infected non-ill subjects have no change in the WBC count. A polymorphonuclear leukocyte response to rhinovirus infection is also seen in the nasal mucosa and nasal secretions.[39,48] As with the changes in peripheral neutrophil count the increase in polymorphonuclear leukocytes is seen in infected symptomatic subjects but not in asymptomatically infected individuals.[48]

The correlation between lymphocytic response to rhinovirus infection and symptomatic illness is less clearly characterized. There are conflicting data about the effect of rhinovirus infection on the peripheral lymphocyte count.[47,49,50] Modest increases in T-lymphocyte concentrations have been reported in both the nasal mucosa and in nasal secretions during rhinovirus infection.[51,52] Few B-lymphocytes were noted in the nasal mucosa.

The role of inflammatory mediators has been the focus of several recent studies of rhinovirus pathogenesis. The similarity between the clinical manifestations of allergic rhinitis and the common cold has prompted repeated attempts to establish the role of histamine in the common cold. Several studies have reported no detectable increase in histamine in nasal secretions during rhinovirus infection.[48,53,54] A recent study reported increases in histamine levels in 4/15 normal subjects and 13/17 subjects with a history of allergic rhinitis following rhinovirus inoculation.[38] Prostaglandin D_2, another mast cell derived mediator, cannot be detected in the nasal secretions of rhinovirus-infected subjects.[38,48] These studies suggest that it is unlikely that histamine or other mast cell mediators make an important contribution to the pathogenesis of rhinovirus colds.

The kinins, bradykinin and lysyl bradykinin, have been found in the nasal secretions of volunteers with rhinovirus colds, both experimentally induced and naturally acquired.[48,55] The concentration and time course of the production of kinins were roughly correlated with the severity and time course of symptoms in these subjects. Subjects who were infected with rhinovirus but who did not develop symptoms did not have an increase in nasal secretion kinin concentration. Intranasal challenge of uninfected volunteers with increasing concentrations of bradykinin resulted in symptoms of nasal obstruction, rhinorrhea, and sore throat.[56] The role of kinins in the pathogenesis of common cold symptoms is less clear, however, in light of the failure of a bradykinin antagonist to alleviate common cold symptoms.[57] Similarly, in a more recent study, steroid therapy significantly reduced the concentration of kinins in nasal washes but had no effect on symptoms.[58]

The interleukins IL-1β, IL-6, and IL-8 have also recently been reported in the nasal secretions of symptomatic subjects with experimental rhinovirus colds.[34,59,60] As with the kinins, the concentration of these proteins increases and then decreases as symptom severity is increasing and then decreasing. The concentrations of IL-6 and IL-8 in nasal secretions appear to be directly correlated with the severity of the common cold symptoms.[60,61] Intranasal challenge of normal volunteers with interleukin-8 produces an influx of neutrophils, a transient increase in nasal resistance to airflow, and a significant increase in nasal symptom scores compared with placebo-challenged subjects.[62] In spite of these data demonstrating an association between symptoms and inflammatory mediators, the role of these mediators in pathogenesis will not be clear until specific inhibitors are available for use in clinical trials.

The neurologic response of the host may also play a role in the pathogenesis of rhinovirus colds. Studies of nasal secretions have shown that glandular secretions in the nose, under the control of cholinergic neurologic pathways, contribute to rhinorrhea especially in the later stages of the illness.[38] Neurologic pathways also appear to be involved in the reactive airway disease associated with rhinovirus infection.[63,64] Inflammatory neuropeptides, such as substance P, play a role in some forms of non-infectious rhinitis however the role of these agents in the common cold remains to be examined.

TREATMENT

A variety of antiviral agents have been studied for the treatment of rhinovirus infections. Several drugs have been identified which have significant in vitro anti-rhinoviral activity.[65–72] When tested in vivo, however, these agents have been ineffective for treatment of rhinovirus infection. In 1984, Abraham and Colonno reported that different rhinovirus serotypes shared the same cellular receptor.[73] Subsequent studies have shown that all rhinoviruses but one attach to cells via only two different receptors.[73,74] The majority of serotypes bind by a single receptor that has subsequently been identified as intercellular adhesion molecule 1 (ICAM-1).[75,76] Blockade of the receptor site on the cells with antibody to ICAM-1 or of the receptor binding site on the virus with soluble ICAM-1 have both been shown to inhibit viral infection in vitro and are potential treatments for the common cold.[74,77–80] The logistics of maintaining an appropriate concentration of either of these proteins in the nasal cavity present formidable obsta-

cles to effective use of these agents, however. Studies of the effect of these agents for treatment of the common cold are in progress.

In the mid-1970s, it was reported that zinc ions inhibit rhinovirus replication.[81] As a result of this observation there have been numerous studies of the efficacy of zinc, given as oral lozenges, for the treatment of common cold symptoms. In spite of the in vitro effect of zinc on virus replication, there has been no detectable effect of zinc lozenges on virus replication in vivo.[82,83] The effect of zinc on symptoms has been inconsistent with some studies reporting dramatic effects on the duration of cold symptoms and other studies finding no effect.[82–86] These studies may not be directly comparable since different formulations of zinc were used in the various studies, however, there is not a direct correlation between the dose of zinc given and the clinical efficacy. A major problem with the interpretation of these studies is the very high frequency (50% to 90%) of side effects in subjects who receive zinc and the difficulty in producing a placebo that is as distasteful and astringent as the active preparation.

Symptomatic therapy remains the mainstay of treatment for the common cold. The use of symptomatic therapies available over-the-counter and directed at specific symptoms of rhinovirus colds has been the subject of some controversy.[87] Although some of these medications have been found to be effective in adults, studies in children have been limited by an inability to accurately measure common cold symptoms in noncompliant subjects. It is reasonable to conclude that the effects of these various preparations should be similar in adults and children. The use of these medications in children, however, must be balanced against the potential side effects of each drug.

Nasal Congestion

Both topical and oral adrenergic agents are effective nasal decongestants.[88–90] Comparative studies have not been done in the common cold; however, it is generally accepted that the topical agents are more potent than the oral drugs.[91] Prolonged use of the topical adrenergic agents should be avoided to prevent the development of rhinitis medicamentosa, an apparent rebound effect when the drug is discontinued. Systemic absorption of the imidazolines (eg, oxymetazoline and xylometazoline) has rarely been associated with bradycardia, hypotension, and coma. The systemic side effects of the oral adrenergic agents are central nervous system stimulation, hypertension, and palpitations. The antihistamines have no effect on nasal congestion.

Rhinorrhea

The treatment of rhinorrhea is primarily by blockade of cholinergic stimulation of glandular secretion. Atropine or ipratropium bromide treatment of experimental rhinovirus colds produced a small decrease in rhinorrhea or nasal mucus weights that was not statistically significant.[92,93] In larger studies of subjects with natural colds, ipratropium produced a 22% to 31% decrease in rhinorrhea compared with placebo.[94–96] Ipratropium has been approved for use for the treatment of rhinorrhea in the common cold. The most common side effects of intranasal ipratropium are nasal irritation and bleeding.

The first generation antihistamines have been used for many years for treatment of rhinorrhea associated with the common cold. A modest but statistically significant effect on rhinorrhea has been found in several small studies in adults, although other studies have failed to detect any therapeutic effect.[97–100] A recent, large study in experimental colds disclosed that clemastine fumarate reduced rhinorrhea by approximately 27% compared with placebo.[101] This observation was subsequently confirmed in a natural cold trial.[102] The second generation or "nonsedating" antihistamines have had no effect on common cold symptoms in a limited number of studies.[103,104] This observation, the absence of histamine in the secretions of most subjects with colds, and the similarity of the response to ipratropium and the antihistamines suggest that the effect of the antihistamines on rhinorrhea is related to the anticholinergic rather than the antihistaminic properties of these drugs. The major side-effects associated with the use of the antihistamines are sedation and drying of the eyes, mouth, and nose.

Sneezing

Sneezing is frequently reported as a symptom during the common cold, however, it is rarely considered the most bothersome symptom by the patient. Antihistamines are effective for treatment of sneezing.[100–102] The mechanism of the effect of antihistamines on sneezing in colds is not known.

Sore Throat

Sore throat is a common symptom early in the course of the cold and is frequently the first symptom noticed by the patient. The sore throat associated with colds is generally not severe and is often described as a "scratchy throat." Treatment with mild analgesics is occasionally indicated, particularly if there is associated myalgia or headache.

Cough

Cough during colds is produced by several different mechanisms and treatment should be directed at the most likely underlying cause. Cough in some patients appears to be due to nasal obstruction or postnasal drip. Cough in these patients is most prominent during the time of greatest nasal symptoms and responds to treatment with an antihistamine/decongestant combination.[105] In other patients, cough may be a result of virus-induced reactive airway disease.[63] These patients may have cough that persists for days to weeks after the acute illness and may benefit from bronchodilator therapy. Cough that persists after the resolution of other cold symptoms or that persists in association with unremitting rhinorrhea may be due to sinusitis and may respond to antibiotic therapy.[106] Nonspecific cough suppression with either codeine or dextro-

methorphan hydrobromide is frequently used; however, the efficacy of these agents has not been demonstrated in the common cold.[107,108] A single study has described a modest effect of nonsteroidal antiinflammatory agents on the acute cough of colds.[109] Expectorants such as guaifenesin are not effective antitussive agents.[110]

A new approach that examined the effect of combining anti-inflammatory and antiviral compounds was reported recently. Gwaltney, reported effective treatment of established rhinovirus infections with a combination of naproxen, ipratropium bromide, and interferon-α2b.[111] The effect of this combination appeared to be greater than the effects usually seen with available common cold therapies.

PREVENTION

The recognition that direct contact was an important mechanism of transmission of rhinovirus led to efforts to prevent contamination of the hands of infected or susceptible individuals. A variety of chemical compounds have been evaluated for efficacy for inactivation of rhinovirus on environmental surfaces or on skin.[112–114] Although some of these agents were found to have activity, a practical and effective hand treatment has not been developed. Facial tissues treated with a combination of citric acid, malic acid, and sodium lauryl sulfate were found to readily inactivate a number of different rhinovirus serotypes and there was some evidence that these tissues would reduce or prevent transmission of virus.[115–117] In spite of the potential utility of this product, it was never made available commercially.

The large number of rhinovirus serotypes has long been recognized as an obstacle to the development of vaccines for protection against rhinovirus infections. The recent observation that most rhinoviruses attach to cells via only two different receptors suggests the potential for preventing infection by receptor blockade.[73,74] Prophylaxis of experimental rhinovirus colds with monoclonal antibody to ICAM-1, the major cellular receptor, delayed but did not prevent infection.[118]

Prevention of rhinovirus infections also has been attempted with a variety of antiviral agents. Pirodavir, a virus capsid binding agent, appears to have some efficacy for prevention of rhinovirus infection although there is no detectable effect on treatment of established infections.[119,120] Similarly, α-interferon is an effective agent for prevention of rhinovirus infections but has no effect on established infection.[121–126] The cost and the side effects of α-interferon preclude its use as an agent for the prevention of rhinovirus colds.[126–130]

CONCLUSION

The relatively mild symptoms and short duration of the common cold have presented a challenge to attempts to provide effective treatment. Currently available treatments that are targeted primarily at reversing the observed effects of the viral infection have limited efficacy. Newer efforts seem likely to result in therapies targeted at key steps in the pathogenesis of the upper respiratory symptoms. These efforts may prove beneficial not only for treatment of the common cold but also for treatment of other viral respiratory syndromes and their complications.

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CME Examination
No 007-004
Questions 1–20, Turner RB. 1997;78:531–40

CME Test Questions

1. The pathogen most commonly associated with the common cold is:
   a. coronavirus
   b. respiratory syncytial virus
   c. rhinovirus
   d. parainfluenza
   e. influenza
2. The average number of colds experienced by adults each year is:
   a. 1–2
   b. 2–3
   c. 4–5
   d. 6
   e. 10–12
3. Most colds appear to be spread from person-to-person by:
   a. direct contact
   b. small particle aerosols
   c. large particle aerosols
   d. fomites
   e. sneezing
4. Small particle aerosol spread of virus from person-to-person has been demonstrated for:
   a. rhinovirus
   b. respiratory syncytial virus
   c. influenza virus
   d. coronavirus
   e. parainfluenza virus
5. Casual contact with a rhinovirus-infected person results in transmission of infection:
   a. <10% of the time
   b. 25% of the time
   c. 50% of the time
   d. 75% of the time
   e. 100% of the time
6. Rhinovirus infection is produced most efficiently by contact between the virus and the:
   a. nasal mucosa
   b. oral mucosa
   c. oropharyngeal tonsils
   d. conjunctiva
   e. tracheal mucosa
7. Rhinovirus is associated with:
   a. focal infection of the lower respiratory tract
   b. focal infection of the upper respiratory tract
   c. generalized infection of the upper respiratory tract
   d. generalized infection of the lower respiratory tract
   e. infection of both the upper and lower respiratory tract
8. Immunity to rhinovirus is most closely associated with:
   a. rhinovirus-specific T-cell mediated immune responses
   b. rhinovirus-specific humoral immune responses
   c. α-interferon in nasal secretions
   d. rhinovirus-specific NK cell activity
   e. nasal mucosal mononuclear cell responses
9. Rhinovirus colds are associated with all except:
   a. increased PMNs in nasal secretions
   b. increased T-lymphocytes in nasal secretions
   c. increased B-lymphocytes in nasal secretions
   d. transudation of serum proteins into nasal secretions
   e. elaboration of inflammatory mediators into nasal secretions
10. Rhinovirus infection produces an increased concentration of PMNs in:
    a. peripheral blood of symptomatic subjects
    b. peripheral blood of asymptomatic subjects
    c. nasal secretions of asymptomatic subjects
    d. peripheral blood of all infected subjects
    e. nasal secretions of all infected subjects
11. Which of the following mediators has consistently been found in the nasal secretions of rhinovirus-infected subjects?
    a. histamine
    b. kinins
    c. prostaglandin D_2
    d. substance P
    e. tumor necrosis factor α
12. There is a direct correlation between nasal secretion concentrations and symptom severity for:
    a. interleukin-1β
    b. interleukin-8
    c. bradykinin
    d. histamine
    e. tumor necrosis factor α

13. The cellular receptor for most rhinoviruses is:
    a. LDL-like protein
    b. ICAM-1
    c. aminopeptidase N
    d. VCAM-1
    e. PECAM-1
14. Nasal congestion associated with colds can be treated effectively with:
    a. topical adrenergic agents
    b. nonsteroidal antiinflammatory agents
    c. antihistamines
    d. cromolyn sodium
    e. intranasal steroids
15. Antihistamines have a beneficial effect on:
    a. rhinorrhea
    b. nasal obstruction
    c. sore throat
    d. sinus congestion
    e. headache
16. Rhinorrhea associated with colds is effectively treated by:
    a. second-generation antihistamines
    b. ipratropium bromide
    c. nonsteroidal antiinflammatory agents
    d. intranasal steroids
    e. kinin antagonists
17. The mechanism of action of the antihistamines for treatment of rhinorrhea associated with colds is related to:
    a. antihistaminic activity
    b. anticholinergic activity
    c. sedation
    d. mast cell stabilization
    e. inhibition of inflammatory interleukins
18. Treatments with proven efficacy for the treatment of cough associated with colds are:
    a. antihistamine/decongestant combinations
    b. dextromethorphan
    c. guaifenesin
    d. intranasal steroids
    e. kinin antagonists
19. Nonsteroidal antiinflammatory agents have a beneficial effect on all except:
    a. rhinorrhea
    b. cough
    c. sore throat
    d. headache
    e. sinus pain
20. Rhinovirus infections can be prevented with:
    a. soluble ICAM-1
    b. α-interferon
    c. antibody to ICAM-1
    d. enviroxime
    e. zinc

Answers to CME examination—Annals of Allergy, Asthma, & Immunology, May 1997 (Identification No. 007-005) Milgrom H and B Bender. Adverse effects of medications for rhinitis. Ann Allergy Asthma Immunol 1997;78:439–46.

1. b	6. a	11. e	16. e
2. a	7. d	12. d	17. e
3. c	8. a	13. e	18. b
4. d	9. b	14. e	19. c
5. b	10. d	15. e	20. d