EVALUATION OF AN ALPHA AGONIST ALONE AND IN COMBINATION WITH A NONSTEROIDAL ANTIINFLAMMATORY AGENT IN THE TREATMENT OF EXPERIMENTAL RHINOVIRUS COLDS*

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DESPITE better understanding of their viral etiologies, colds remain a major cause of morbidity.[1] Therapeutic trials with antiviral agents,[2] such as intranasal enviroxime[3-5] or interferons,[6-8] have yielded discouraging results in rhinovirus colds. Currently, treatment of colds is limited to attempts at symptomatic relief, yet the pathogenic mechanisms responsible for symptom production in rhinovirus colds remain poorly understood.[2] One approach to unravelling the pathogenesis of these infections is through investigation of

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pharmacologic interventions. Prior studies at the University of Virginia have evaluated anticholinergic[9] and antihistaminic drugs,[10,11] as well as glucocorticosteroids.

Alpha-adrenergic agents, such a oral decongestants and anti-inflammatory-analgesic drugs, are among the medications most frequently taken for the relief of cold symptoms. However, few studies have evaluated these agents in colds of documented viral etiology. Oral sympathomimetic agents have been shown to improve subjective symptoms[12] and nasal patency[13-14] in patients with natural colds. On the other hand, Stanley et al.[15] reported the effects of early aspirin treatment of experimental rhinovirus colds and found no significant decreases in infection or illness rates compared with placebo, but did report significant increases in the rate of virus shedding in nasal wash specimens of the aspirin recipients. In a smaller series, Mogabgab and Pollock[16] observed no increase in virus isolation in pharyngeal washings on the first few days after the development of symptoms following experimental rhinovirus challenge in those treated with aspirin compared with placebo. If nonsteroidal anti-inflammatory agents alter host responses to increase the frequency of virus shedding during colds, this effect could increase the risk of transmitting infection to contacts.

Nonsteroidal anti-inflammatory agents such as ibuprofen have inhibitory effects on polymorphonuclear leukocyte migration and function.[17-22] These drugs also inhibit the release[23] and biologic effects [24-27] of kinins. Such activities may be relevant to symptom pathogenesis, since rhinovirus colds are associated with significant increases in the concentrations of polymorphonuclear leukocytes in nasal epithelium[28] and nasal secretions,[29] as well as in kinin concentrations in nasal wash specimens.[29]

In this randomized, double-blind, placebo-controlled study we used an alpha agonist, pseudoephedrine, alone and in combination with the nonsteroidal anti-inflammatory drug ibuprofen in treating experimental rhinovirus colds. A preliminary study found that administration of ibuprofen 200 mg four times daily beginning four hours before rhinovirus challenge did not significantly reduce the development of cold symptoms, but may have enhanced the decongestant effect of oral pseudoephedrine begun at 48 hours after challenge (unpublished observations). In this study we determined the effect of these agents on the frequency, duration, and quantity of virus recovery in experimentally induced rhinovirus colds, as well as their effects on subjective and objective measures of illness when treatment was initiated after virus challenge.

MATERIALS AND METHODS

Subjects. Fifty-eight healthy adults with a serum neutralizing antibody titer of ≤1:2 to the challenge rhinovirus were eligible for participation after giving informed consent in a form approved by the University of Virginia Human Investigation Committee. Subjects were excluded if they had upper respiratory symptoms or fever within one week prior to initiation of the study; a history of active or chronic sinusitis, asthma, or recent hay fever; required use of antihistamines, systemic or topical nasal decongestants, aspirin or other nonsteroidal anti-inflammatory drugs, monoamine oxidase inhibitors or phenothiazines; had a history of hypersensitivity to aspirin or other anti-inflammatory drugs, pseudoephedrine or other sympathomimetics; were pregnant or lactating; or would be smoking during the study period.

Virus challenge. Intranasal rhinovirus challenge was administered in two inocula over a 15 minute period by a calibrated pipette (50 ul per nostril) with the subject supine. Subjects remained supine for five minutes after each inoculum and were asked not to blow their noses for one half hour. Based on susceptibility determined on initial serum samples, type 39 (200-600 $TCID_{50}$ per subject) was administered to 29 subjects and Hank's strain (an untyped rhinovirus, 20-66 $TCID_{50}$ per subject) was given to the remaining 29 subjects.

Experimental design. The subjects were isolated in motel rooms for five days beginning 24 hours after rhinovirus challenge. Based on pretreatment nasal airway flow rates, they were randomly assigned to receive two identically appearing capsules containing pseudoephedrine HCl 60 mg and ibuprofen 200 mg, pseudoephedrine HCl 60 mg and placebo, or both placebos (supplied by Vicks Research Center, Shelton, CT). Treatment was initiated 30 hours after virus inoculation. Two doses were given the first day after virus challenge at 6:30 P.M. and 11:30 P.M. On the subsequent four days, drug was administered four times daily (8:30 A.M., 1:30 P.M., 6:30 P.M., 11:30 P.M.) for a total of 18 doses. Subjects were discharged from the motel on the sixth day after inoculation and seen in follow-up two weeks later, at which time sera were obtained to measure antibody response to the challenge virus.

Measures of infection. Nasal washings were collected prior to virus inoculation and each morning on days two through six after challenge. Washings were cultured for rhinovirus on human fibroblast cells by previously described methods,[30] and isolates were identified as type 39 or Hank's rhino-

virus by neutralization with type-specific antisera. Infection was defined as seroconversion (fourfold or greater rise in homotypic serum antibody to the challenge virus) and/or recovery of the challenge virus from nasal washings on at least one day. On selected specimens rhinovirus titers were determined by culture of serial 10-fold dilutions of once frozen (−70°C) and thawed original nasal wash specimens. Titers were calculated by the Kärber method.[31]

Measures of illness. The frequency and severity of illness were determined by twice daily recording of the volunteers' symptoms: nasal (discharge, obstruction, sneezing), throat (sore throat, hoarseness, cough) and systemic (headache, chills, feverishness, malaise) on a four point scale (0-3, absent to severe). The higher of the two daily ratings was used as the score for that day. Colds were defined as present based on previously described criteria.[32] The need for concomitant medications dispensed for cold symptoms was also recorded. Subjects were also questioned twice daily concerning the presence of any unusual symptoms potentially referable to drug toxicity.

Objective measures of illness severity included morning and evening oral temperatures; daily collection of nasal tissues for tissue counts and determination of nasal secretion weights (postchallenge days two-six) by previously described methods;[33] and nasal patency measurements by anterior rhinometry[13,14] prior to and 45 and 90 minutes after administration of the 8:30 A.M., 1:30 P.M., and 6:30 P.M. drug doses. Blood pressure was measured three times (7:30 A.M., 10:00 A.M., 8:00 P.M.) and pulse rate once (7:30 A.M.) daily in all subjects during the study period.

Data analysis. All subjects were included in the evaluation of tolerance, whereas analysis of efficacy was based only on infected subjects. Measures of illness (including symptom data, mucus weights, tissues, and duration of illness) were analyzed using analysis of variance by the Kriskal-Wallis test. Paired interactions between groups were examined when the overall p value was less than 0.10. Temperature, blood pressure, and pulse analysis utilized analysis of variance for treatment effects. Mean systolic and diastolic blood pressures were obtained by averaging the two A.M. values from each study day and then averaging this value with the P.M. value. Data comparing proportions were analyzed by the Fisher's exact test.

For nasal patency, the measurement preceding the first drug dose served as the baseline from which subsequent changes were calculated. The area under the curve for each treatment group was determined for each day during the hours from 8:30 A.M. to 10:00 P.M.

TABLE I. INFECTION RATES, VIRUS SHEDDING, AND ILLNESS RATES IN RHINOVIRUS-CHALLENGED VOLUNTEERS TREATED WITH PSEUDOEPHEDRINE, PSEUDOEPHEDRINE PLUS IBUPROFEN, OR PLACEBO

Treatment (N)	*Number (%) of subjects*			*Days of virus recovery/total days of observation*	*Colds (% of infected subjects)**
	Infected	*Shed virus*	*Seroconvert*		
Pseudoephedrine plus ibuprofen (23)	18 (78)	18 (78)	12 (52)	56	61
Pseudoephedrine alone (23)	22 (96)	20 (87)	17 (74)	58	77
Placebo (10)	9 (90)	7 (70)	69	89	

*Infected subjects; pseudoephedrine plus ibuprofen n = 18, pseudoephedrine alone n = 22, placebo n = 9

RESULTS

Subjects. Fifty-six subjects completed the study. One subject (pseudoephedrine plus ibuprofen recipient) was excluded from the analysis because the preinoculation viral culture showed infection with a wild type rhinovirus and another subject withdrew prematurely for personal reasons (placebo recipient). Of the evaluable subjects, 23 received pseudoephedrine alone, 23 received pseudoephedrine plus ibuprofen, and 10 received placebo. The groups were similar with regard to mean age (placebo, 20 years; pseudoephedrine, 21; pseudoephedrine plus ibuprofen, 21). The gender distribution did differ between groups (placebo, 70% female; pseudoephedrine, 52%; pseudoephedrine plus ibuprofen, 26%, $p=0.04$, pseudoephedrine plus ibuprofen vs. placebo), but our earlier studies have not found this a significant variable in infection or illness of experimental rhinovirus challenge (Hayden, F.G. and Gwaltney, J.M., Jr., unpublished observations). Of the 56 evaluable subjects, 28 received type 39 virus and 28 received Hank's strain. The proportion of subjects in each group receiving each virus type was the same (rhinovirus type 39 was the challenge virus for 50% of placebo recipients, 48% of pseudoephedrine recipients, and 52% of recipients of pseudoephedrine plus ibuprofen).

Infection and virus shedding. Infections occurred at similar rates in all three treatment groups (Table I). Two subjects (both recipients of pseudoephedrine alone) seroconverted but did not shed virus. Virus shedding occurred with similar frequency in each of the treatment groups, and the percent of observation days on which virus was recovered did not differ between the groups (Table I). The peak frequency of shedding occurred on

TABLE II. SYMPTOM SCORES, MUCUS WEIGHTS, AND NASAL TISSUE COUNTS IN RHINOVIRUS-INFECTED VOLUNTEERS TREATED WITH PSEUDOEPHEDRINE, PSEUDOEPHEDRINE PLUS IBUPROFEN, OR PLACEBO

	Symptom scores (days 1–6 post-challenge)					
Treatment (N)	*Total*	*Nasal*	*Throat*	*Headache/ systemic*	*Mucus weight (gram/5d)*	*Nasal tissue count (no/5d)*
Pseudoephedrine plus ibuprofen (18)	12 ± 9*	7 ± 5†,‡	4 ± 4	1 ± 2*	19 ± 28*	43 ± 50
Pseudoephedrine alone (22)	15 ± 10**	10 ± 5**	3 ± 3	3 ± 4*	16 ± 16‖	53 ± 48
Placebo (9)	29 ± 23	14 ± 5	8 ± 13	7 ± 7	27 ± 19	63 ± 53

Note: All values are expressed as mean ± S.D.
*$0.01<p<0.05$, versus placebo
**$0.05<p<0.10$, versus placebo
†$p<0.01$, versus placebo
‡$p=0.09$, versus pseudoephedrine
‖$p=0.05$, versus placebo

postchallenge day two in each group, and no differences existed between the groups in the frequency of shedding on any postchallenge day. In subjects who shed virus, the mean ±S.D. duration of virus shedding was 3±1 days for placebo recipients, 3±2 days for pseudoephedrine recipients, and 3±1 days for recipients of pseudoephedrine plus ibuprofen. Viral titers did not differ significantly between groups on the second postchallenge day, which was the day of greatest frequency of shedding. The mean±S.D. titers were 1.0±0.8 $\log_{10}$ $TCID_{50}$/0.2 ml nasal wash for placebo recipients (n=7), 0.7±0.5 for recipients of pseudoephedrine alone (n=18), and 0.6±0.2 for recipients of pseudoephedrine plus ibuprofen (n=14).

Illness frequency and severity. In infected subjects colds developed in 89% of placebo recipients, 77% of pseudoephedrine recipients, and 61% of subjects receiving pseudoephedrine plus ibuprofen. The mean ±SD time during which infected subjects assessed they had a cold was 3±2 days in recipients of pseudoephedrine alone ($p=0.09$ vs placebo and 2±1 days in recipients of pseudoephedrine plus ibuprofen ($p<0.01$ vs placebo), compared with 4±2 days in placebo recipients. There was also a tendency favoring both treatment groups in subjective illness severity. Of subjects with colds, 29% of pseudoephedrine recipients and 18% of recipients of pseudoephedrine plus ibuprofen rated their colds to be of moderate or marked severity, compared with 50% placebo recipients.

Total symptom scores were reduced by 48% in pseudoephedrine recipients and 59% in recipients of pseudoephedrine plus ibuprofen compared to placebo (Table II). The peak in symptom scores occurred on postvirus challenge

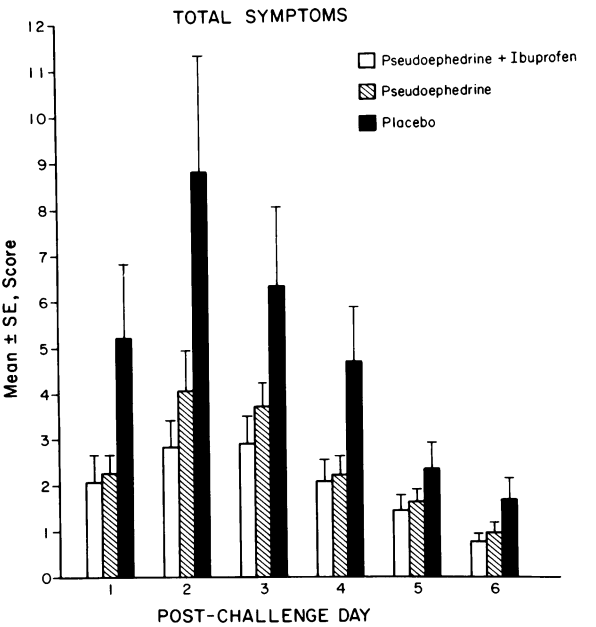

Fig. 1. Total symptoms by study day after rhinovirus challenge in recipients of pseudoephedrine, pseudoephedrine plus ibuprofen, or placebo. Treatment was begun in the evening of the first postchallenge day. For day one, symptoms were recorded 90 minutes after the first drug dose ($p < 0.05$, days two and four, pseudoephedrine plus ibuprofen versus placebo).

day two (second day of treatment) (Figure 1), at which time pseudoephedrine recipients averaged 53% lower, and pseudoephedrine plus ibuprofen recipients averaged 68% lower scores than placebo recipients. Symptom scores were significantly reduced in recipients of pseudoephedrine plus ibuprofen on days two and four compared to placebo. Cumulative nasal scores and systemic scores were significantly reduced in recipients of pseudoephedrine plus ibuprofen compared to placebo (Table II). Pseudoephedrine alone showed similar trends. However, no significant differences existed between the two drug groups for total symptoms. Nasal symptoms tended to be reduced in recipients of pseudoephedrine plus ibuprofen compared with pseudoephedrine alone ($p=0.09$). The specific symptom of nasal congestion (stuffiness) was significantly reduced by pseudoephedrine plus ibuprofen (mean $\pm$S.D. score/5 days, 4 ± 3) compared with placebo (7 ± 2, $p<0.05$), whereas the reduction by pseudoephedrine alone (6 ± 4) did not differ from placebo. The symptom of nasal discharge was not significantly reduced in either group (pseudoephedrine plus ibuprofen 2 ± 2, pseudoephedrine 2 ± 2) compared with placebo (4 ± 3).

TABLE III. USE OF ACETAMINOPHEN AND INDICATION FOR ADMINISTRATION IN RHINOVIRUS-INFECTED SUBJECTS

Treatment	No. infected subjects	No. of subjects taking acetominophen (%)			
		All conditions	Headache	Fever	Other pains
Pseudoephedrine plus ibuprofen	18	2 (11)*	1 (6)*	1 (6)	0
Pseudoephedrine alone	22	4 (18)*	4 (18)**,†	1 (5)†	0
Placebo	9	8 (89)	6 (67)	0	2 (22)‡

*$p<0.01$, versus placebo
**$p=0.03$, versus placebo
†One subject was administered acetaminophen for headache and fever on separate days
‡Backache, eye pain

Nasal discharge weights were 41% lower in the pseudoephedrine group ($p=0.05$) and 30% lower in the pseudoephedrine plus ibuprofen group ($p=0.04$), compared with placebo (Table II). There were no significant differences in change in temperature between groups during the study period (data not shown). Only two subjects (one pseudoephedrine and one pseudoephedrine plus ibuprofen recipient) had a temperature greater than 100°F on one or more measurements.

A total of 14 subjects reported conditions for which a study nurse administered acetaminophen during the observation period. The condition for which this was administered most frequently was headache, followed by feverishness and other pains. Of infected subjects, 18% of pseudoephedrine recipients and 11% of pseudoephedrine plus ibuprofen recipients required acetaminophen, compared with 89% of placebo recipients ($p<0.01$ either treatment group vs placebo) (Table III).

Nasal patency. Recipients of pseudoephedrine plus ibuprofen showed trends toward improved nasal patency from pretreatment baseline flow rates on days 4($p=0.08$) and 5($p=0.06$), whereas the degree of change from baseline was minimal in the pseudoephedrine and placebo groups (Figure 2). The overall and daily patency tended to be greater in the recipients of pseudoephedrine plus ibuprofen compared to placebo. Patency in recipients of pseudoephedrine alone on most days was intermediate. However, analysis of the mean values for each day and for the entire treatment period was confounded by high variability between subjects.

Tolerance. Both pseudoephedrine alone and pseudoephedrine plus ibuprofen were generally well tolerated. No subjects withdrew from the study due to adverse drug effects. Possible adverse effects are listed in Table IV. Symptoms potentially referable to sympathetic stimulation tended to be increased among recipients in both pseudoephedrine groups compared to pla-

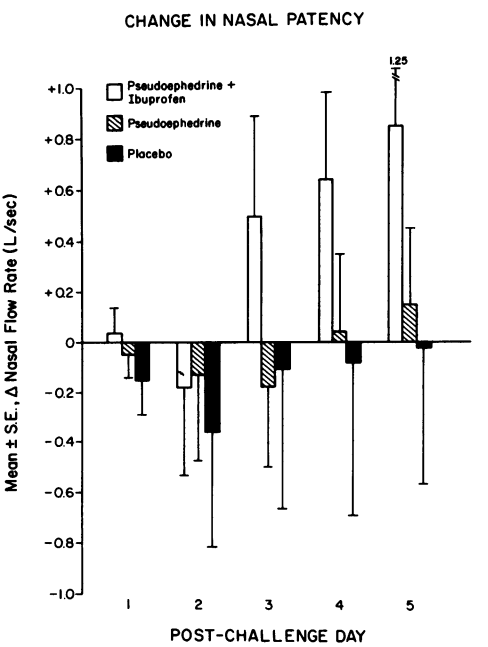

Fig. 2. Change in nasal patency from baseline by study day after rhinovirus challenge in recipients of pseudoephedrine, pseudoephedrine plus ibuprofen, or placebo. Treatment was begun in the evening of the first postchallenge day. Nasal airflow rates were determined nine times daily for days two–five, and three times on day one beginning 45 minutes after treatment was started ($0.05 < p < 0.1$, pseudoephedrine plus ibuprofen versus baseline. On days four and five.

cebo. Mean pulse rates over the treatment period did not differ between groups (placebo, 72±4 per minute; pseudoephedrine, 71±8; pseudoephedrine plus ibuprofen, 69±6), nor was the change from baseline prestudy pulse rates. The percent of subjects with an elevation of pulse rate of

TABLE IV. POSSIBLE ADVERSE EFFECTS OF TREATMENT OF RHINOVIRUS COLDS WITH PSEUDOEPHEDRINE, PSEUDOEPHEDRINE PLUS IBUPROFEN, OR PLACEBO IN ALL SUBJECTS

		Number (percent) of subjects					
	No. subjects	*Any*	*Light-headedness*	*Difficulty sleeping*	*Lethargy*	*Indigestion*	*Other*
Pseudoephedrine plus ibuprofen	23	6 (26)	2 (9)*	1 (4)**	0	0	4 (17)**,†
Pseudoephedrine alone	23	4 (17)	2 (9)*	0	1 (4)	1 (4)	0
Placebo	10	2 (20)	0	1 (10)	1 (10)	0	0

*Sum of all pseudoephedrine recipients (4/46) was not significantly different from placebo (0/10)

**One subject reported both difficulty sleeping and "dry mouth"

†One subject reported each: "dry mouth," "feeling hyper," "feeling more awake," and "flushed face and increased heart rate." In this last subject increased pulse rate was not documented.

greater than 10 beats per minute over their baseline on at least one occasion did not differ between groups (placebo 20%, pseudoephedrine 13%; pseudoephedrine plus ibuprofen 17%). However, because these pulse measurements were obtained in the early morning before dosing, they do not assess the maximal effect of these drugs.

The mean systolic blood pressures during the study period were not significantly different between groups (placebo 115±6 mm Hg, pseudoephedrine 118 ±7, pseudoephedrine plus ibuprofen 119±6). Compared with a single prestudy baseline measurement (placebo, 116±8; pseudoephedrine, 119±10; pseudoephedrine plus ibuprofen, 114±10), the systolic blood pressure over the study period was increased in the ibuprofen plus pseudoephedrine group compared with pseudoephedrine alone ($p=0.02$) and tended to be higher than the placebo group ($p=0.06$). There was no difference between the pseudoephedrine and placebo groups in change in systolic blood pressure. Mean diastolic blood pressures during the study period did not differ between groups or from pretreatment baselines values.

DISCUSSION

This study is part of a series of investigations using pharmacologic interventions to study the pathogenesis of rhinovirus colds and is the first to examine the efficacy of combination symptomatic therapy for experimental rhinovirus colds. We used both subjective and objective parameters to evaluate an alpha agonist, pseudoephedrine, alone and in combination with the nonsteroidal anti-inflammatory agent ibuprofen as treatment for induced rhinovirus colds. Illness severity was reduced by both pseudoephedrine alone and in combination with ibuprofen. Total symptom scores were significantly reduced by pseudoephedrine plus ibuprofen, and a similar trend was found with pseudoephedrine alone. Nasal symptom scores tended to be reduced in recipients of pseudoephedrine plus ibuprofen compared with pseudoephedrine alone, but other subjective and objective measures of efficacy did not detect significant differences between the active treatment groups. Rhinorrhea, as reflected in nasal mucus weights, was significantly less in either treatment group compared with placebo. Nasal patency tended to be greater among the recipients of pseudoephedrine plus ibuprofen compared with placebo or with pseudoephedrine alone. Pseudoephedrine recipients in this study, in contrast to prior investigation,[14] did not show a significant improvement in nasal patency compared with placebo.

Another criterion by which efficacy can be evaluated in this study is the frequency of administration of concomitant medications for symptom relief.

Compared with infected placebo recipients, significantly fewer pseudoephedrine or pseudoephedrine plus ibuprofen recipients received acetaminophen for headache or other reasons (Table III). It is noteworthy that headache requiring acetaminophen was reduced in recipients of pseudoephedrine alone, despite the lack of known analgesic or anti-inflammatory properties. One explanation is that headaches attributable to sinus and nasal congestion were reduced by its decongestant activity. Two (11%) of the infected subjects receiving pseudoephedrine plus ibuprofen were given acetaminophen for headache or fever. It is noteworthy that the dose of ibuprofen used (200 mg) was relatively low, in that greater analgesic efficacy may be achieved with higher dosages.[34]

When virus shedding was examined, we observed that the addition of ibuprofen did not increase the percent of subjects shedding virus, duration of shedding, or titers of virus recovered from shedders on the second day after challenge. This finding is in contrast with the observations of Stanley et al.,[15] who reported increased frequency of shedding in aspirin recipients following experimental rhinovirus challenge. If the findings of Stanley et al.[15] are confirmed, it would suggest that ibuprofen and aspirin may have different mechanisms of action in rhinovirus colds. In the study by Stanley et al.[15] aspirin alone, 600 mg three times daily, had minimal benefits on clinical symptoms. Our study, however, did not include a separate group treated with only ibuprofen, and thus we cannot directly assess the clinical or virologic effects of ibuprofen alone.

The mechanisms by which rhinovirus infection causes respiratory symptoms are not fully understood. Analysis of cellular responses has revealed influxes of polymorphonuclear leukocytes in the nasal mucus[29] and nasal epithelium[28] early in experimental rhinovirus colds. Additionally, polymorphonuclear leukocyte counts in nasal lavage specimens from subjects with experimental rhinovirus colds correlate with the severity of illness.[29] In vitro ibuprofen has been shown to inhibit several polymorphonuclear leukocyte functions, including directed and random migration, adherence, release of lysosomal enzymes, and superoxide generation.[17,18] Decreased polymorphonuclear leukocyte adherence has been observed in humans at four and 24 hours following a single 300 mg dose.[21] Decreased granulocyte aggregation in response to the synthetic chemotactic peptide, N-formyl-Met-Lue-Phe (FMLP), with altered kinetics of the polymorphonuclear leukocyte receptor-FMLP interaction is also observed in ibuprofen concentrations achievable in the blood with oral therapy.[20]

Studies addressing the role of inflammatory mediators have shown that

histamines do not play a major role in production of nasal symptoms,[29,35] whereas kinins, especially bradykinin, may be important mediators in experimental rhinovirus colds.[29] In infected symptomatic volunteers the concentration of kinins in nasal secretions correlates with the severity of illness,[29] and intranasal administration of exogenous kinins to healthy adults results in nasal obstruction, sore throat, and rhinorrhea.[36] The role of prostaglandins or leukotrienes as potential mediators of rhinovirus illness is not well defined. Levels of prostaglandin D_2 were not found to be elevated in three symptomatic volunteers with experimental rhinovirus colds.[29]

Intriguing in this context is the relationship between prostaglandins, bradykinin, and prostaglandin inhibitors. Bradykinin-induced prostacyclin stimulation in man, presumably from vascular endothelium, is rapidly inhibited by a 600 mg oral dose of aspirin.[24] Nonsteroidal anti-inflammatory agents also interfere with the release and activity of bradykinin into rat paw perfusate in response to noxious and neuronal stimulation[23] and have peripheral effects inhibiting bradykinin-mediated stimulation of rabbit spinal sensory neurons.[25,26] Thus, a beneficial effect of nonsteroidal anti-inflammatory agents on upper respiratory symptoms might theoretically derive from inhibition of cyclooxygenase and the resulting decreased production of prostaglandins.

It would be tempting to speculate that if kinin effects and/or local polymorphonuclear leukocyte influx are important in triggering or amplifying respiratory symptoms in rhinovirus colds, nonsteroidal anti-inflammatory agents could interfere with these mechanisms. However, except for a trend toward reduced nasal symptom scores, our study did not document a significant clinical effect when ibuprofen was added to pseudoephedrine during the late incubation phase of rhinovirus infection. Well controlled clinical trials with ibuprofen or related agents given early in the course of rhinovirus infections, along with analysis of kinin and polymorphonuclear leukocyte content in the nasal mucosa and secretions, would be necessary to further evaluate this hypothesis.

This study also found a decrease in nasal mucus weights in pseudoephedrine and pseudoephedrine plus ibuprofen recipients compared with placebo. To our knowledge, this is the first study to demonstrate a decrease in nasal secretions in rhinovirus colds by an alpha agonist. If true, it is likely this effect is a result of vasoconstriction in the nasal passages causing a decrease in transudation across the nasal mucosa. Prior rhinometric evaluations in subjects with rhinitis have shown a marked nasal decongestant effect of oral pseudoephedrine, with peak activity paralleling that of topically applied

ephedrine, another alpha agonist,[14] although the patency measurements in our study failed to show such an effect.

Both pseudoephedrine and ibuprofen were generally well-tolerated. Symptoms potentially referable to increased sympathomimetic activity were reported by several subjects receiving pseudoephedrine (Table IV). There were no adverse effects (i.e., gastric upset) directly attributable to ibuprofen. Compared with phenylpropanolamine and ephedrine, other commonly used oral decongestants, pseudoephedrine appears to have a lower potential for cardiac side effects.[37,38] In a single dose study of 18 subjects aged 19-33 years, pseudoephedrine 60 mg had no effect on diastolic or systolic blood pressure or pulse rate, whereas dosages of 120 or 180 mg did significantly raise the latter two.[39] In our study using pseudoephedrine 60 mg four times daily, systolic blood pressure was significantly increased, compared to baseline measurements, in the pseudoephedrine plus ibuprofen group but not the pseudoephedrine alone group. These results were not associated with clinical adverse effects in our relatively young volunteer population and could reflect the variability in obtaining a single blood pressure determination for use as a baseline. An alternative explanation is that a synergistic or additive effect on blood pressure may have been achieved by the combination of pseudoephedrine plus ibuprofen. Nonsteroidal anti-inflammatory agents can affect the constrictor response to vasopressors and lead to sodium retention.[40,41] Several recent studies have examined the effect of ibuprofen at doses of 1,200-2,400 mg daily on blood pressure in normotensive[42] and stable hypertensive adults.[41,43] These studies, which used dosages higher than our study, did not detect significant changes after one week of ibuprofen treatment but several found increases at three[41] and four[43] weeks.

Thus, we have shown that pseudoephedrine 60 mg four times daily improves certain parameters of illness severity following experimental rhinovirus infection. The addition of ibuprofen 200 mg four times daily may have provided additional clinical benefit, specifically with respect to nasal symptoms and patency, but the combination was not clearly superior to pseudoephedrine alone. Larger sample sizes would be required to demonstrate statistical differences between the treatment groups. From a clinical perspective, it would be important to know whether the beneficial effects shown in this study of pseudoephedrine or pseudoephedrine plus ibuprofen initiated at 30 hours after infection would also be achieved if therapy were delayed until the onset of symptoms. Additionally, future studies of nonsteroidal anti-inflammatory agents alone may aid in our understanding of the pathogenesis of rhinovirus colds.

SUMMARY

The pathogenesis of symptoms of the common cold and their optimal treatment are incompletely understood. To evaluate the role of an oral alpha agonist alone and in combination with a nonsteroidal anti-inflammatory drug in the treatment of experimental rhinovirus colds, 58 subjects were randomized to receive pseudoephedrine 60 mg alone, pseudoephedrine 60 mg plus ibuprofen 200 mg, or placebo, four times daily for 4 1/2 days beginning 30 hours after intranasal rhinovirus inoculation under double-blind conditions. The frequencies of infection, colds occurrence, and viral shedding did not differ significantly between the groups. Total symptom scores were reduced by 59% by pseudoephedrine plus ibuprofen ($p<0.05$) and 48% by pseudoephedrine alone compared with placebo. Nasal symptom scores tended to be lower in recipients of pseudoephedrine plus ibuprofen compared with pseudoephedrine alone ($p=0.09$), but other parameters showed no significant treatment differences between the groups. Rhinorrhea, as determined by nasal secretion weights, was significantly reduced in both treatment groups compared to placebo. Nasal patency measurements tended to show the greatest improvement in recipients of pseudoephedrine plus ibuprofen. Therapy was clinically well tolerated. The results suggest that an oral alpha agonist is effective in modifying certain manifestations of experimental rhinovirus infection and that the addition of a nonsteroidal anti-inflammatory drug may provide additional benefit in nasal symptoms and patency. Studies involving large numbers of patients with natural colds are needed to determine the clinical significance of these findings.

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Erratum

In Volume 64, page 1036, the heading should read: Volume 64, 1988.