Effectiveness of Clemastine Fumarate for Treatment of Rhinorrhea and Sneezing Associated with the Common Cold

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Limited data support the use of first-generation antihistamines for treatment of the common cold. The purpose of this study was to test the effectiveness of clemastine fumarate, a first-generation antihistamine, for treatment of sneezing and rhinorrhea associated with naturally occurring common colds. Four hundred three subjects (202 clemastine fumarate recipients and 201 placebo recipients) who reported new onset (<24 hours) of cold symptoms that included rhinorrhea or sneezing were studied. At baseline (day 1), the mean symptom-severity scores ± SEM for the clemastine fumarate and placebo groups were not significantly different. The mean rhinorrhea-severity score ± SEM was not different on day 2; however, on day 3, the mean rhinorrhea-severity score ± SEM was 1.02 ± 0.07 for the clemastine fumarate group and 1.39 ± 0.07 for the placebo group ($P < .001$). This treatment effect persisted on day 4. A significant effect on sneezing was noted on days 2–4. Sedation occurred in 14% of the clemastine fumarate–treated subjects and 1.5% of the placebo-treated subjects ($P < .0001$).

Viral upper respiratory tract infection is the most common illness in humans. Although it is generally a mild illness, the common cold is responsible for more days of work and school absence than all other illnesses combined [1]. There is also an enormous cost associated with the common cold for physician visits and the purchase of cough and/or cold remedies by consumers. The symptomatic treatment of cold symptoms currently relies on decongestants for nasal congestion, antitussives for cough, analgesics for headache and myalgia, and antihistamines for rhinorrhea and sneezing. These agents are available without prescription and are widely used [2]. The paucity of data that support the use of these various agents for treatment of the common cold was the subject of a recent review [3].

Rhinorrhea and sneezing are important components of the common cold. Several studies have been conducted to establish the efficacy of antihistamines for the treatment of these symptoms. Although these studies generally found no, or very modest, treatment effects, critical review suggests that the studies did not have sufficient experimental power to conclusively establish a lack of efficacy [4–7]. A decrease in both rhinorrhea and sneezing following treatment with clemastine fumarate, a first-generation antihistamine, was reported in a recent large study of experimental rhinovirus colds [8]. The purpose of this study was to determine the efficacy of clemastine fumarate for treatment of rhinorrhea and sneezing in subjects with natural colds.

Materials and Methods

Subjects. Male or female subjects, 18 years of age and older, were recruited at three study sites: the University of Virginia (Charlottesville), Hackensack University Medical Center (Hackensack, NJ), and the Medical University of South Carolina (Charleston). The protocol was approved by the Institutional Review Boards at the respective institutions, and all subjects gave written informed consent for participation.

Surveillance phase. Subjects in the surveillance phase of the study were recruited by newspaper and posted advertisements and were paid for participation. Approximately 1,000 subjects were kept under surveillance at the three study sites at all times from September 1994 to April 1995. As subjects discontinued participation or were enrolled in the treatment study, additional subjects were recruited to maintain the surveillance population. All subjects recorded the presence or absence of headache, muscle ache, runny nose, sneezing, stopped-

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Informed consent was obtained from all subjects who participated in this study, and the guidelines for human experimentation of the U.S. Department of Health and Human Services and those of the institutions where the study was conducted were followed in the conduct of this study.

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up nose, sore throat, scratchy throat, cough, hoarseness, postnasal drip, feverishness, chilliness, and feeling sick in a diary that was completed daily and reviewed by study staff at 2- to 3-week intervals. The subjects were instructed to contact the study staff with the first occurrence of any of these common cold symptoms to determine eligibility for the treatment phase of the trial.

Treatment phase. Subjects who reported runny nose and/or sneezing, had at least two different symptoms, had recorded symptoms in their diary for no more than 1 day, and responded ''Yes'' to the question ''Have you had the onset of a cold within the last 24 hours?'' were eligible for enrollment in the treatment study. Females of childbearing age were required to have a negative pregnancy test and use effective birth control. Subjects with underlying illnesses that might be exacerbated by antihistamines or that might affect the assessment of common cold symptoms were excluded from the study. Subjects who were taking medications that might interact with antihistamines or alter common cold symptoms were also excluded from the study. Subjects with a history of seasonal or perennial allergic rhinitis must have responded ''No'' to the question ''Are you suffering from allergies at the present time?''.

Study medications. Study subjects received either 1.34 mg of clemastine fumarate or identically appearing placebo tablets. The active and placebo tablets were randomly distributed in sequentially numbered blister packs provided to each study site. Subjects were then given the blister packs in numerical order as they were admitted to the treatment phase of the study. The initial dose of study medication was administered by a study nurse on day 1 of the study between 8:00 A.M. and noon. The second dose on day 1 was self-administered ~12 hours after the first dose. On study days 2–5, subjects took their medication at ~8:00 A.M. and 8:00 P.M. Compliance with the study medications was encouraged by the study staff during daily telephone contact, and the empty blister packs were collected to confirm that all medications had been taken. Subjects were instructed to take no other common cold remedies while receiving the study medication.

Study procedures. Subjects participating in the surveillance phase of the study who contacted the study center and reported common cold symptoms were evaluated in person. Eligibility criteria were reviewed, and an assessment of baseline symptoms was done. A symptom-severity score of 0–4, corresponding to absent, mild, moderate, severe, and very severe symptoms, respectively, was assigned to each of the symptoms of sneezing, rhinorrhea, nasal obstruction, sore throat, cough, headache, malaise, chilliness, and postnasal drip. Each morning on subsequent study days (days 2–5), subjects were contacted by telephone and asked to evaluate the severity of these symptoms over the previous 24-hour period. Subjects were instructed to take the morning dose of study medication after reporting their symptoms. In addition, on day 2, each subject was asked to record the severity of symptoms 4, 8, and 12 hours after the morning dose of study medication. On study day 6, each subject was again evaluated in person to review any adverse events and to conduct a final evaluation of symptoms.

Data analysis. The demographics and symptom severity at the baseline evaluation were compared to document the comparability of the treatment groups. A one-way analysis of variance (ANOVA) was used to compare age across treatment groups. Race, gender, sneezing severity, and rhinorrhea severity were compared by using either the χ^2 or Fisher's exact test.

The primary analysis for assessment of the effectiveness of clemastine fumarate was defined, a priori, as comparison of rhinorrhea- and sneezing-severity scores for the treated and control subjects on days 2 and 3 of the study. Comparison of other common cold symptoms in the two groups was done as a secondary analysis. The treatment groups were compared on days 2–4 by assessment of the change from baseline in response to the study medication. The analysis of these results was done with a three-way ANOVA with treatment arm and study site as the between-groups factors and the interactive symptom scores on days 2–6 as the repeated-measures factor. For analysis of the day 2–timed symptom-severity scores, a similar ANOVA model was used except that the different times (4, 8, and 12 hours after the morning dose) served as the repeated-measures factor, and treatment contrasts were conducted at these times.

All available data, including data for subjects who subsequently withdrew from the study, were included in the analyses. To validate the assumptions underlying the ANOVA, the data were also analyzed with nonparametric tests. The significance levels were essentially unchanged, and only the results of the ANOVA are presented.

A post hoc analysis of the change in sneezing severity from baseline for those subjects who reported at least moderate (symptom-severity score, ≥ 2) sneezing at the time of enrollment and the change in rhinorrhea severity from baseline in those subjects who had at least moderate rhinorrhea at the time of enrollment was done by using the methods described above. The statistical significance of differences in incidence of side effects in the treatment and placebo groups was determined by using a one-sided Fisher's exact test.

The sample size was based on previous data on experimental colds [8] and produced an estimate of 331 subjects per group, with $P_\alpha = .05$ and $P_\beta = .8$ for a two-tailed test. The study protocol provided for two blinded interim analyses and a final analysis. The interim analyses were examined by an independent data review panel after enrollment of approximately one-third of the planned number of subjects and again after enrollment of approximately two-thirds of the planned number of subjects. Treatment differences were considered statistically significant if the P level was $\leq .021$ at the second interim analysis. This P_α at the second analysis, with corresponding prospective adjustments of the P_α at the first interim analysis and final evaluation, provided overall protection against type I error at the P level of .05.

The a priori criterion for the effectiveness of clemastine fumarate for treatment of common cold symptoms was that the

Table 1. Demographic characteristics on 403 subjects at enrollment who received either clemastine fumarate or placebo as treatment of rhinorrhea and sneezing associated with the common cold.

Characteristic	Clemastine fumarate recipients (n = 202)	Placebo recipients (n = 201)	P value
Mean age ± SEM* (y)	35.1 ± 0.64	33.7 ± 0.58	.10
No. of whites: no. of blacks or others†	168:34	165:36	.78
No. of females: no. of males†	159:43	155:46	.70
Mean sneezing-severity score ± SEM‡	1.17 ± 0.06	1.32 ± 0.06	.39
Mean rhinorrhea-severity score ± SEM‡	1.73 ± 0.07	1.65 ± 0.07	.37

* Analyzed by using a one-way analysis of variance.
† Analyzed by using a χ^2 test.
‡ Analyzed by using the Fisher's exact test.

mean change in symptom-severity score for rhinorrhea and sneezing would be greater in the treatment group than in the placebo group on either day 2 or day 3 at a statistically significant level. The study met the criterion for statistical significance and was terminated after the second interim analysis. The data analysis revealed no difference in symptom severity or treatment effect by site of enrollment.

Results

Four hundred three subjects were enrolled in the treatment phase of the study; 202 received clemastine fumarate, and 201 received placebo. Subject enrollment was similar at the three study sites, with 164 subjects enrolled at the University of Virginia, 123 enrolled at the Medical University of South Carolina, and 116 enrolled at Hackensack University Medical Center. Approximately 40% of the subjects who reported cold symptoms while under surveillance met the enrollment criteria for the treatment study. The most common reasons for not enrolling subjects were the presence of symptoms for >24 hours, a report of only a single symptom, or the absence of either rhinorrhea or sneezing as a symptom.

The demographic characteristics of the subjects enrolled in the treatment and placebo groups were similar (table 1). There were no significant differences in mean symptom-severity scores between the two groups before treatment. There were also no significant differences in demographic characteristics or baseline symptom severity at the study sites. The enrollment of subjects was evenly distributed throughout the study period with the exception of February and March, when 182 (45%) of the subjects were enrolled.

Twenty-three subjects, 16 who received clemastine fumarate and seven who received placebo (P = .08), withdrew from the study before completion. Six subjects, all in the treatment group, withdrew because of excessive drowsiness. Two subjects in the treatment group withdrew when their symptoms resolved and one subject in the placebo group withdrew because of treatment failure. Fourteen subjects, eight in the treatment group and six in the placebo group, withdrew for reasons unrelated to their illness or the study medication.

Effect of clemastine fumarate on sneezing. The mean symptom-severity scores ± SEM for sneezing in the treatment and placebo groups at baseline were 1.17 ± 0.06 and 1.32 ± 0.06, respectively (P = .39). On day 2, the mean sneezing-severity scores ± SEM for the two groups were 0.74 ± 0.06 and 1.16 ± 0.07, respectively (P < .001). These decreases are a mean change from baseline of 37% for the treatment group and 11% for the placebo group (P = .007). The mean symptom-severity scores ± SEM for sneezing that were recorded 4, 8, and 12 hours after the morning dose of medication on day 2 were also lower (P ≤ .002) for the treatment group. This treatment effect persisted with statistically significant results on days 3 and 4 (figure 1). The 143 subjects (65 who received clemastine fumarate and 78 who received placebo) who reported sneezing of at least moderate severity at baseline revealed similar findings. Treatment reduced sneezing severity in this group of subjects 22.7%, 23.4%, and 21.5% relative to the placebo group on days 2, 3, and 4, respectively.

Effect of clemastine fumarate on rhinorrhea. The mean symptom-severity scores ± SEM for rhinorrhea at baseline were 1.73 ± 0.07 and 1.65 ± 0.07 for the clemastine fumarate- and placebo-treated subjects, respectively (P = .37). On day 2, the mean rhinorrhea-severity scores ± SEM for the two groups were 1.46 ± 0.07 and 1.58 ± 0.08, respectively (P = .24). These decreases are a mean change from baseline of 16% for the treatment group and 4% for the placebo group (P = .1). The mean symptom-severity scores ± SEM for rhinorrhea were lower for the clemastine fumarate–treated subjects 4, 8, and 12 hours after the morning dose on day 2; these differences were statistically significant at 8 hours (P = .002) and 12 hours (P = .01).

The effect of clemastine fumarate was more pronounced on day 3, when the mean symptom-severity score ± SEM for rhinorrhea was 1.02 ± 0.07 for the treatment group and 1.39 ± 0.07 for the placebo group (P < .001) and the mean change from baseline was 42% for the treatment group and 16% for the placebo group (P < .001). This treatment effect persisted on day 4 (figure 2). A post hoc analysis of the 225 subjects (120 clemastine fumarate recipients and 105 placebo recipients) who reported rhinorrhea of at least moderate severity when they were enrolled in the treatment phase of the study produced similar results. Treatment reduced rhinorrhea severity in this group of subjects 21.2% and 17.7% relative to the placebo group on days 3 and 4, respectively.

Effect of clemastine fumarate on secondary treatment variables. No treatment effect was seen on any of the secondary variables with the exception of nasal congestion. On day 3, compared with baseline severity scores, the mean nasal conges-

tion–severity score ± SEM was improved for the treatment group (−0.13 ± 0.09) and was worse for the placebo group (+0.27 ± 0.09) ($P < .001$). Statistically significant differences in nasal congestion severity were not detected on the other days of observation.

Side effects. The subjects were asked to report any potential side effects of the medication. In response, 56 (28%) of the clemastine fumarate recipients and 30 (15%) of the placebo recipients complained of adverse events. These adverse events were judged by the blinded investigators to be related to the treatment in 44 (22%) of the subjects in the clemastine fumarate group and 14 (7%) of the subjects in the placebo group ($P < .001$). The difference was due mainly to sedation-related events (drowsiness, sleepiness, and tiredness) that occurred in 28 (14%) of the subjects who received clemastine fumarate and three (1.5%) of the subjects who received placebo

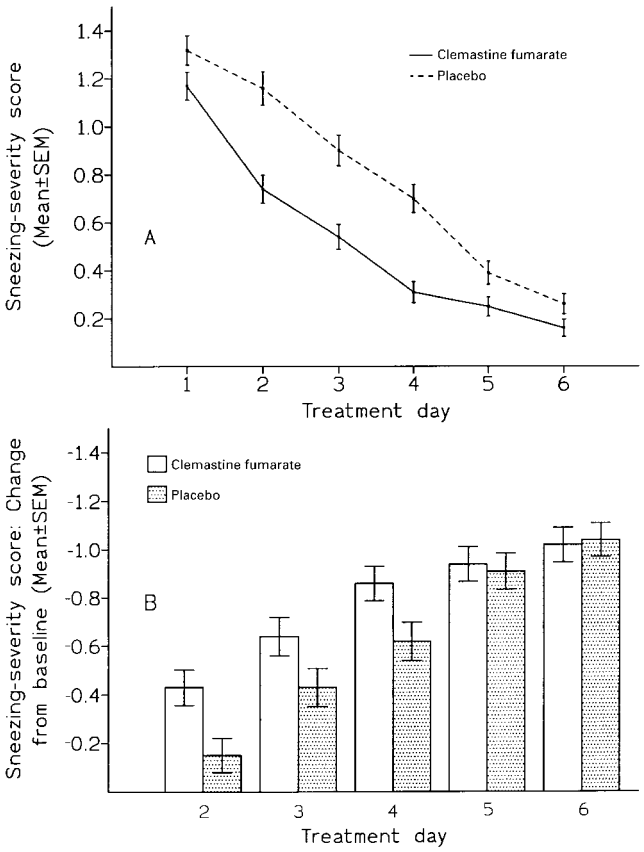

Figure 1. Comparison of the effect of clemastine fumarate and placebo on sneezing associated with the common cold. *A*. Mean sneezing-severity score ± SEM by day. Comparison of clemastine fumarate–treated subjects with placebo-treated subjects revealed statistically significant differences ($P < .021$) in mean sneezing-severity scores ± SEM on treatment days 2–4. *B*. Change in mean sneezing-severity scores ± SEM from baseline by day. Comparison of clemastine fumarate–treated subjects with placebo-treated subjects revealed significantly greater changes ($P < .021$) in mean sneezing-severity scores ± SEM from baseline for the clemastine fumarate–treated subjects on treatment days 2 and 4.

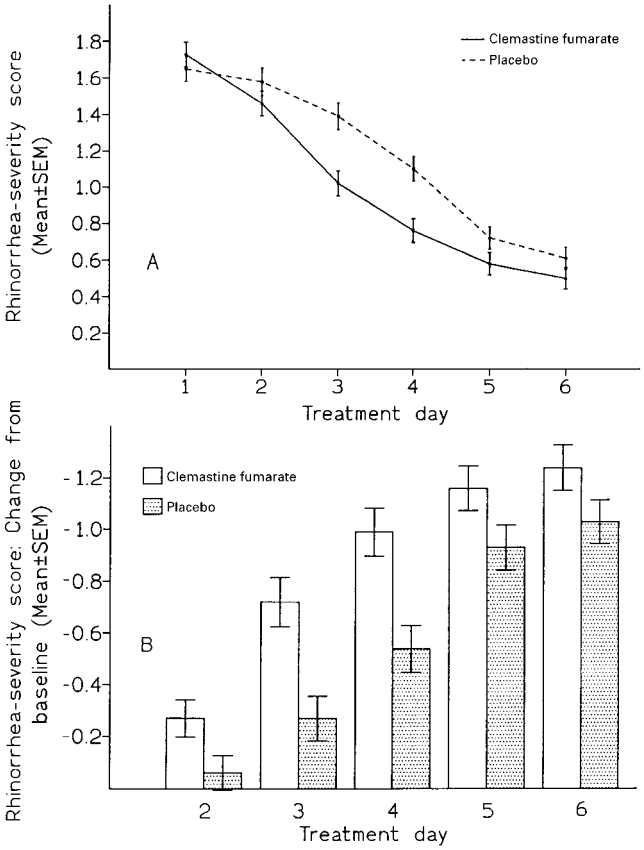

Figure 2. Comparison of the effect of clemastine fumarate and placebo on rhinorrhea associated with the common cold. *A*. Mean rhinorrhea-severity score ± SEM by day. Comparison of clemastine fumarate–treated subjects with placebo-treated subjects revealed statistically significant differences ($P < .021$) in mean rhinorrhea-severity scores ± SEM on treatment days 3 and 4. *B*. Change in mean rhinorrhea-severity scores ± SEM from baseline by day. Comparison of clemastine fumarate–treated subjects with placebo-treated subjects revealed significantly greater changes ($P < .021$) in mean rhinorrhea-severity scores ± SEM from baseline for the clemastine fumarate–treated subjects on treatment days 3 and 4.

($P < .0001$). The number of subjects who withdrew from the study because of sedation-related events was higher in the clemastine fumarate group than in the placebo group (six vs. zero, respectively; $P = .015$). Most treatment-related adverse events were of either mild or moderate severity; however, 11 events in the clemastine fumarate group and six events in the placebo group were reported to be severe.

Discussion

The results of this study demonstrate that clemastine fumarate is effective treatment for the nasal symptoms of rhinorrhea and sneezing in patients with naturally occurring common colds. Relative to placebo, clemastine fumarate reduced sneezing severity 26% and 22% and rhinorrhea 12% and 26% on

days 2 and 3, respectively. Similar results were seen when the analysis was limited to those subjects who presented with at least moderate symptom severity. This result for natural colds complements the results reported from a similar study of the effect of clemastine fumarate on induced colds [8]. In that study, clemastine fumarate was shown to reduce sneezing-severity scores (50%), sneeze counts (57%), rhinorrhea scores (27%), and nasal mucus weights (35%). The difference in the apparent size of the treatment effect between the studies done in the natural setting and those done on induced colds appears to be a result of the less controlled conditions inherent in the natural setting. Similar findings have been noted with other therapeutic agents [9, 10].

Subjects were enrolled in the treatment phase of this study on the basis of the presence of symptoms typical of acute viral upper respiratory tract infection. Allergic rhinitis is also typically associated with sneezing and rhinorrhea, although other components of the common cold symptom complex such as cough and sore throat are generally absent. In patients with allergic rhinitis, antihistamines reduce rhinorrhea by 20%–40% compared with placebo [11–14]. The inadvertent inclusion of significant numbers of subjects with allergic rhinitis in our study would have potentially affected our assessment of efficacy; we do not believe that this occurred in our study.

All patients enrolled in the treatment phase of the study were under surveillance prior to enrollment and at the time of enrollment were explicitly asked whether they were having a cold. The surveillance phase of the study would be expected to identify those subjects who had undiagnosed perennial rhinitis, and in a previous study on natural colds that used the surveillance model [15], subjects were found to be able to accurately differentiate colds from allergic rhinitis. The risk that enrollment of patients with allergic rhinitis influenced the results of our study is further reduced by the fact that most subjects were enrolled during the winter months, when the incidence of seasonal allergic rhinitis would be expected to be low.

The mechanism of action of the therapeutic effect of the first-generation antihistamines on the common cold is not clear. There is little information that addresses the mechanism of action of the antihistamines for the treatment of sneezing. The limited data regarding the mechanism of the effect on rhinorrhea suggest that the effect may be due to the anticholinergic activity of these drugs. Histamine was not detectable in nasal wash in two studies of the common cold [16, 17]. A more recent study [18] found that histamine levels were increased during colds in four of 15 subjects; however, there was no correlation between histamine levels and nasal or serum protein concentration in the nasal secretions. The suggestion that histamine is not involved in the production of rhinorrhea is further supported by reports of the ineffectiveness of the nonsedating antihistamines (which have potent antihistamine activity but lack significant anticholinergic activity) for treatment of rhinorrhea [19, 20]. These studies of treatment of the common cold with the nonsedating antihistamines involved subjects with natural colds, and it would be interesting to study these drugs under more controlled conditions with experimentally induced colds.

The hypothesis that the effect of the first-generation antihistamines on rhinorrhea is mediated by their anticholinergic activity is also supported by the similarity of the effect of these drugs and that of ipratropium bromide, which has anticholinergic but not antihistaminic activity [9, 10, 21]. Despite these data suggesting an anticholinergic mechanism of action, an antihistaminic effect cannot be ruled out. Allergic and nonallergic patients experimentally infected with rhinovirus have more sneezing and rhinorrhea in response to histamine challenge than uninfected controls [22]. These results suggest that increased sensitivity to histamine normally present in the nasal secretions might result in the increase of rhinorrhea and sneezing associated with the common cold. If this is the case, it is plausible that the effectiveness of antihistamines in the symptomatic treatment of the common cold may be due to their reduction of the effect of normal histamine levels.

Although histamine and/or cholinergic mechanisms appear to play a role in rhinorrhea and sneezing, the constellation of symptoms that constitute the common cold syndrome appears to result from a complex pathogenesis that involves a number of mediators as well as neurological mechanisms [23–26]. Thus, regardless of the mechanism of action, antihistamines would not be expected to have a direct effect on the nasal congestion, sore throat, headache, or cough associated with the cold. As a result, a detectable effect on a global symptom assessment was not expected in this study and was not included as an endpoint.

The demonstration of a statistically significant effect of antihistamines for treatment of sneezing and rhinorrhea does not address the issue of the clinical relevance of the observed effect. We believe that the results of this study were clinically meaningful. The definition of a clinically significant endpoint was established before the execution of the study and was met before enrollment of the entire calculated sample size. Also relevant to assessment of the clinical significance of the results is the fact that the endpoints in this study were improvements in subjective symptom-severity scores. The determination of clinical significance is more difficult when objective endpoints, such as sneezing counts or nasal mucus weights, are reported without an assessment of whether the changes in these endpoints are perceptible to the subjects. In this study, the symptom-severity scores directly assessed the subjects' perception of their symptom burden.

A final aid to assessment of the clinical relevance of these results is a comparison to size of the treatment effect in other illnesses or with other therapies that are generally accepted as clinically meaningful. The magnitude of the treatment effects seen in this study is comparable with that previously reported in studies of the treatment of allergic rhinitis with antihistamines [11–14]. The treatment of common cold symptoms with

ipratropium bromide, recently approved by the U.S. Food and Drug Administration for treatment of rhinorrhea in patients with colds, also produces a similar reduction in rhinorrhea severity [9].

Safety is an important consideration for therapies for the common cold. Since the symptoms are relatively mild and self-limited and of short duration, cold remedies must be safe and free of serious side effects. In this study, the frequency of side effects, especially sedation-related effects, associated with clemastine fumarate was higher than that associated with placebo. The frequency of sedation in this study was comparable with that reported in previous clinical trials with the first-generation antihistamines [12, 14, 27].

The increased incidence of sedation-related side effects in the clemastine fumarate–treated subjects has potential implications for interpretation of the results of the study. The subjective assessment of symptoms of these mild and self-limited illnesses is readily biased when subjects are unblinded by an inadequate placebo control [28, 29]. In this study, subjects who developed drowsiness could have correctly concluded that they were receiving the active treatment. Although sedation occurred significantly more frequently in the clemastine fumarate–treated subjects, only 14% reported this side effect. The subjects in this study were not aware that rhinorrhea and sneezing were the primary variables of efficacy. The lack of an effect of clemastine fumarate on the other common cold symptoms recorded as part of the symptom-severity score suggests that the observed effect on rhinorrhea and sneezing was not the result of bias introduced by unblinding of the subjects.

The results of this study provide a basis for informed decisions about the use of antihistamines as therapy for the common cold. It is likely that other antihistamines with anticholinergic activity similar to that of clemastine fumarate would have a similar therapeutic effect. As with any common cold remedy, the decision to use these agents rests with the patient and their physician and must take into consideration the severity of the target symptoms, the expected benefit, the potential occurrence of side effects, and cost.

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