



Producers of Quality
Nonprescription Medicines and
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CONSUMER HEALTHCARE PRODUCTS ASSOCIATION

Formerly Nonprescription Drug Manufacturers Association

November 22, 2000

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane Room 1061
Rockville, MD 20852

***RE: Docket No. 76N-052H Cold, Cough, Allergy, Bronchodilator,
and Antiasthmatic Drug Products for Over-the-Counter Human Use;
Reopening if the Administrative Record for Antihistamine Drug Products***

Dear Sir or Madam;

These comments are submitted by the Consumer Healthcare Products Association (CHPA) in response to the Food and Drug Administration (FDA) reopening the administrative record for over-the-counter (OTC) antihistamine drug products to accept comments on recommendations concerning the use of these products to relieve symptoms of sneezing and runny nose due to the common cold. This action was published in the *Federal Register* on August 25, 2000.

CHPA is a 119 year-old trade association representing the manufacturers of over-the-counter drug products and dietary supplements. CHPA members market all of the major national and private label brands of antihistamine containing cough/cold products.

Summary Position

The agency has invited comments on its tentative position that there is sufficient basis to include the use of OTC antihistamines for relief of sneezing and runny nose due to the common cold in the final monograph for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products. CHPA has submitted data and participated in the advisory committee process that has led to this conclusion. Since the agency's last actions on this issue, no new data has emerged that would question these conclusions. **CHPA supports the agency's conclusion and intention to adopt into a final rule the indication, relief of sneezing and runny nose due to the common cold, as a monograph claim for antihistamine-containing OTC drug products.**

Detailed Comments

Consumers rely on OTC cold medications to relieve a variety of symptoms of the common cold, including the target symptoms for OTC antihistamines -- runny nose and sneezing. Surveys indicate that the common cold represents a leading cause of morbidity and loss of

76N-052H

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work and school days in the United States. Runny nose and sneezing occur concurrently in a large number of cold sufferers and are part of the symptom complex associated with the common cold. Table 1 shows reporting rates of runny nose and sneezing from several nationally projectable consumer research studies that have been submitted to the FDA in CHPA's November 1995 presentation to the Nonprescription Drugs Advisory Committee.

Table 1
Colds Attitude and Tracking Data
Retrospective

Symptom	CRAUTS '86/'87 *	C/FMI '88/'89 *	CSCCM '94 *
Runny Nose	62-71 %	69 %	68-79 %
Sneezing	68-77 %	NA	47-51 %
Nasal Congestion	NA	82 %	66-73 %
Cough	61-71 %	73 %	59-65 %
Sore Throat	NA	59 %	55-56 %

CRAUTS 86/87: Colds Remedy Attitude and Use Tracking Study
1986/7

C/FMI 88/89: Colds/Flu Incidence Monitor, 1988/9

CSCCM 94: Cold & Sinus Category Communications Monitor, 1994

NA = not available

Consumer need and demand for antihistamine-containing OTC drug products indicate their effectiveness. However, substantial clinical evidence also exists to support the marketing of OTC antihistamines for the cold symptoms of runny nose and sneezing. The agency states in the August 25, 2000 *Federal Register* notice that sufficient basis currently exists for all Category I antihistamine ingredients to have the indication of relief of sneezing and runny nose due to the common cold. This conclusion is rational because ingredients in this class have pharmacologic actions and therapeutic applications in common and are generally discussed together and generally recognized as effective H1 antagonists with antimuscarinic effects as well. Populations of consumers exist who would benefit from either of these effects on cold symptoms and therefore the agency's conclusions are justified.

Runny nose and sneezing are symptoms proposed by FDA as indications for antihistamines early in the OTC Review and currently proposed for inclusion in the antihistamine final monograph. The pharmacologic actions of the various Category I, first generation, OTC antihistamines are similar and data from ingredients in this pharmacologic class can be extended to all Category I antihistamines. This is the same conclusion that was reached by FDA in the Tentative Final Monograph for antihistamines.

As a part of FDA's review, in 1992 CHPA submitted a review of published and unpublished clinical evidence to support the effectiveness of OTC antihistamines against the target cold symptoms of runny nose and sneezing. At that time, fifteen published and unpublished

clinical studies were submitted supporting the effectiveness of first generation OTC antihistamines for sneezing and runny nose associated with the common cold. Overall, the clinical database is supportive of the conclusion that first generation OTC antihistamine are effective for the relief of sneezing and runny nose associated with the common cold. Specifically in the 1992 submission, fifteen clinical studies report statistically significant outcomes (10 studies) or directionally positive outcomes (5 studies) of OTC recommended doses of first generation antihistamines against sneezing and/or runny nose. The magnitude of beneficial effect in treating these target symptoms is in the same range as that provided by the other types of OTC therapies in relief of symptoms appropriate for self-care.¹

Coincident with this activity, the Procter & Gamble Company initiated a multi-center European-based clinical trial of 7.5 mg doxylamine in cold sufferers². The results of this study were submitted to FDA by CHPA in March 1994. This study (R-002/92) was a double blind, placebo controlled trial in which the 688 entered subjects used a categorical scale to score the symptom severity of runny nose and sneezing.³ The results of this trial demonstrated statistically significant reductions in the severity of the two target symptoms, sneezing and runny nose.

In 1992, the agency formed a task force that consisted of agency staff, FDA Staff Fellows, and outside consultants, to assess the available data on OTC antihistamines that would help resolve the issues of effectiveness and extrapolation for Category I antihistamines. The task force performed a meta-analysis on studies meeting specific inclusion criteria, comparing active ingredients to placebo for both increment scores (change from baseline) and goal of therapy (50 percent reduction or complete cessation of symptom). The symptoms evaluated by the task force were runny nose and sneezing on each of 2-study days. Using these parameters and analyses, the task force found that the antihistamines have an effect on runny nose and sneezing in the early phases of the common cold.

The meta-analysis and the information in the CHPA's submissions in 1992 and 1994 are consistent. The meta-analysis represents a conservative approach with a very rigorous definition of clinical significance. It also provides a convergence of clinical significance across different methodologies. This method of analysis was an appropriate and

¹ Several published studies report no statistical effect of antihistamines on sneezing or runny nose. However, because of design limitations leading to poor compliance, underdosing, poor definition of cold symptoms, and potential observer bias, these studies do not represent reliable evidence to refute the agency's conclusion that first generation OTC antihistamines are effective in colds. These studies were taken into account in the FDA's meta-analysis within the inclusion/exclusion criteria for inclusion in the analysis.

² This study has been published in the *American Journal of Respiratory and Critical Care Medicine*. 149(4):A602, April 1994.

³ The study was originally designed to run over two distinct cold seasons; however, the protocol allowed an interim analysis at the end of the first season with a provision to terminate the study. In order to protect the overall level of significance at 5%, the individual interim analyses was performed at the 3% level. As a result of the observation of significant findings, the study was terminated at the interim analysis stage.

scientifically valid approach to demonstrate the efficacy of antihistamines for relief of symptoms of the common cold.

The task force presented the results of its meta-analysis to a joint meeting of the Nonprescription Drugs Advisory Committee and the Pulmonary-Allergy Drugs Advisory Committee held on November 15, 1994. CHPA presented the clinical data and consumer information supporting the use of antihistamines for the relief of runny nose and sneezing and commented favorably on the meta-analysis. The Committees were not asked for a recommendation at the time of the meeting. The following year, on November 16, 1995, the Committees met again and discussed the analysis. CHPA again presented to the committee. At this meeting, the Committees concluded that the meta-analysis supports the use of chlorpheniramine maleate and doxylamine succinate to relieve the symptoms of runny nose and sneezing associated with the common cold. However, the Committees voted against extrapolating the data on these two ingredients to all Category I antihistamines because they had insufficient data regarding the active mechanism of these drugs in relief of symptoms of the common cold.

CHPA does not agree with the advisory committee's conclusions. Adequate information is known about the first generation antihistamines to permit extrapolation across members of the class for efficacy in the common cold. The principle mechanism of action of first generation antihistamines in producing clinical benefit for sneezing and runny nose associated with the common cold has been postulated to be via intrinsic anticholinergic activity that produces a "drying effect" by blocking the parasympathetic innervation of the nasal mucous and serous glands in the mucosa and/or a direct effect on central mechanisms of the sneezing reflex. This mechanism is supported by high affinity for muscarinic/cholinergic receptor binding for first generation antihistamines (Kubo et al. 1987 – submitted in CHPA's November 1995 submission). Since CHPA's last submission, we have reviewed the literature and found one published report further supporting the Agency's approach to extend the relief of runny nose and sneezing indication to all GRAS/E active ingredients in the antihistamine monograph: Affinities of Brompheniramine, Chlorpheniramine, and Terfenadine at the Five Human Muscarinic Cholinergic Receptor Subtypes. 1999. Yasuda, S.U., and Yasuda, R.P. *Pharmacotherapy*. 19(4):447-451.

The study by Yasuda and Yasuda evaluates the affinities of brompheniramine and chlorpheniramine in comparison with atropine at the five human muscarinic receptor subtypes expressed on CHO cells transfected with the individual receptor subtypes. Since muscarinic anticholinergic mechanisms are believed to be responsible for the efficacy of first generation antihistamines related to runny nose due to the common cold, the paper's demonstrated muscarinic receptor binding affinity of these antihistamines for human muscarinic receptors supports the agency's hypothesis that the efficacy of the first generation antihistamines is related to antimuscarinic activity. A copy of this report is enclosed.

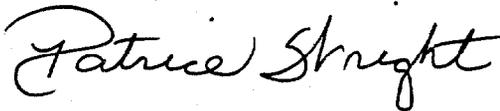
Conclusion

In conclusion, the available clinical data reviewed by FDA provide sufficient evidence to support the clinical benefit of OTC antihistamines for sneezing and runny nose associated with the common cold. The magnitude of the benefits of OTC antihistamines for runny nose and sneezing associated with the common cold is comparable to their acknowledged benefits in allergy sufferers. FDA's conclusions are consistent with the definition for effectiveness for OTC monograph ingredients: "Effectiveness means a reasonable expectation that, in a significant proportion of the target population, the pharmacological effect of the drug, when used under adequate directions for use and warnings against unsafe use, will provide clinically significant relief of the type claimed." [(CFR 21: 330.10(4)(ii); emphasis added]

CHPA has submitted detailed comments and data to the agency on June 15, 1992 and March 3, 1994. In addition, the Association submitted detailed testimony at the November 15, 1994 and November 16, 1995 meetings of the Nonprescription Drugs Advisory Committee. All of these activities have been in support of an indication for relief of runny nose and sneezing associated with the common cold. CHPA's submissions support the Agency's current conclusions that all OTC monographed antihistamines effectively relieve the common cold symptoms of sneezing and runny nose in consumers.

With the information in the public record, CHPA and its member companies support the agency's conclusions and look forward to the inclusion of an indication for the relief of sneezing and runny nose in the monograph for antihistamine drug products. Please feel free to contact my office should you have any additional questions or if we may be of further assistance.

Sincerely,



Patrice B. Wright, Ph.D.
Director, Pharmacology & Toxicology

Enclosure: Affinities of Brompheniramine, Chlorpheniramine, and Terfenadine at the Five Human Muscarinic Cholinergic Receptor Subtypes. 1999. Yasuda, S.U., and Yasuda, R.P. *Pharmacotherapy*. 19(4):447-451.

RESEARCH IN BASIC SCIENCE

Affinities of Brompheniramine, Chlorpheniramine, and Terfenadine at the Five Human Muscarinic Cholinergic Receptor Subtypes

Sally Usdin Yasuda, Pharm.D., Robert P. Yasuda, Ph.D.

Anticholinergic effects are presumed to be the mechanism for the efficacy of chlorpheniramine in symptomatic relief of the common cold. Terfenadine, a second-generation antihistamine, reportedly lacks anticholinergic side effects. We evaluated affinities of two commonly used over-the-counter antihistamines, brompheniramine and chlorpheniramine, as well as terfenadine in comparison with atropine at the five human muscarinic cholinergic receptor subtypes using CHO cells stably transfected with the individual subtypes. Atropine was more potent than all three drugs at m1-m5 ($p < 0.01$). No significant difference was observed between chlorpheniramine and brompheniramine. Atropine, brompheniramine, and chlorpheniramine could not discriminate between m1-m5. Terfenadine demonstrated subtype selectivity at m3. In vitro comparisons in human muscarinic receptor subtypes could potentially be used to predict clinical anticholinergic effects of antihistamines and to target receptor-specific effects of such agents. (Pharmacotherapy 1999;19(4):447-451)

Brompheniramine and chlorpheniramine are two structurally similar and commonly used histamine H₁-receptor antagonists (antihistamines) that have been available for almost 50 years. Terfenadine is a second-generation antihistamine that once ranked among the top 20 most frequently prescribed drugs in the United States.¹ Despite a great deal of clinical experience with them, their basic and clinical pharmacology is incompletely characterized.

Antihistamines are primarily given to treat symptoms of allergic rhinitis based on their

activity at the H₁ receptor. Brompheniramine and chlorpheniramine are alkylamine antihistamines and appear to have comparable efficacy providing symptomatic relief of allergic rhinitis.²⁻⁴ Both drugs have similar side effects including anorexia, drowsiness, and sedation.⁵ Adverse effects attributed to blockade of muscarinic cholinergic receptors include dry mouth and urinary retention.⁵ The prominent presumed anticholinergic effects of older antihistamines led to development of newer antihistamines with fewer of these side effects.

Terfenadine is a piperidine antihistamine structurally dissimilar from brompheniramine and chlorpheniramine, which has been administered to treat allergic rhinitis. Like other second-generation antihistamines, it is not sedating and, unlike the classic antihistamines, does not cause dry mouth and urinary retention.⁵

For more than 40 years, controversy has surrounded treatment of symptoms of the common cold with antihistamines.⁶⁻⁹ The only

From the Department of Pharmacology, Georgetown University Medical Center, Washington, D.C. (both authors).

Supported by Whitehall Robins Healthcare, Madison, NJ.

Presented as a poster at the annual meeting of the American Society for Clinical Pharmacology and Therapeutics, New Orleans, April 1, 1998.

Address reprint requests to Sally Usdin Yasuda, Pharm.D., Department of Pharmacology, Med-Dent Building, SE404, Georgetown University Medical Center, 3900 Reservoir Road, NW, Washington, DC 20007.

Table 1. Displacement of [³H]-N-methyl-scopolamine by Antagonists at Human m1-m5 Receptor Subtypes in Vitro

	(-) Log IC ₅₀ (M) (mean ± SD; n=3)				
	m1	m2	m3	m4	m5
Atropine	8.3 ± 0.50	8.17 ± 0.43	8.23 ± 0.45	8.22 ± 0.33	8.17 ± 0.92
Brompheniramine	4.72 ± 0.08	4.49 ± 0.35	4.30 ± 0.24	4.17 ± 0.26	4.54 ± 0.34
Chlorpheniramine	4.59 ± 0.24	4.77 ± 0.09	4.28 ± 0.24	4.11 ± 0.30	4.55 ± 0.25
Terfenadine	5.06 ± 0.24	5.07 ± 0.43	5.28 ± 0.04 ^a	4.51 ± 0.05	4.95 ± 0.35

^ap<0.01 versus atropine, brompheniramine, and chlorpheniramine at m3; p<0.05 versus terfenadine at m4.

antihistamines with this Food and Drug Administration-approved indication are chlorpheniramine, doxylamine, and clemastine. The putative mechanism for their beneficial effect in this setting is their affinity for muscarinic cholinergic receptors. Studies evaluated the anticholinergic potency of several antihistamines using muscarinic cholinergic receptors from rat brain.¹⁰ However, the potency of brompheniramine, chlorpheniramine, and terfenadine at human muscarinic receptor subtypes has not been described.

The purpose of this study was to characterize the selectivity and relative potencies of brompheniramine, chlorpheniramine, and terfenadine at the five known subtypes of the human muscarinic cholinergic receptor. Characterization of affinities of the agents for the receptor would help explain similarities or differences among them in terms of clinical effect.

Methods

Muscarinic Receptor Assay

Muscarinic receptor membranes were prepared from Chinese hamster ovary (CHO) cells stably transfected with individual subtypes of human muscarinic cholinergic receptors m1-m5. The CHO cells were grown in medium containing DMEM/F12 supplemented with 10% fetal bovine serum, glutamine 2 mM, penicillin 100 U/ml, and streptomycin 0.1 mg/ml, and were grown at 37°C in humidified air supplemented with 8% CO₂. Confluent cells were harvested by scraping and homogenized in TE buffer (10 mM Tris HCl, pH 7.4, 1 mM EDTA) with a Tekmar Tissuemizer (setting 60) for 10 seconds. Homogenates were centrifuged at 30,000 x g for 20 minutes. Pellets were resuspended in TE buffer at a protein concentration of 2 mg/ml. Protein concentrations of membranes from each subtype used in each assay were 35 µg m1, 5 µg m2, 25 µg m3, 45 µg m4, and 67 µg m5. Protein concentrations were determined using the BCA protein assay.

[³H]-N-methyl-scopolamine binding to membrane preparations was performed in 0.3 ml total volume containing the indicated amount of membranes (see above), 0.6 nM [³H]-N-methyl-scopolamine, and indicated amounts of H₁-antagonist. Nonspecific binding was determined in the presence of 10 µM atropine. Drugs were diluted in buffer or dimethylsulfoxide (DMSO) for terfenadine. Atropine was diluted in DMSO when used to define nonspecific binding for terfenadine studies. Samples were incubated for 2.5 hours at 25°C. The reaction was stopped by adding 10 ml ice-cold TE buffer. Samples were filtered by vacuum filtration through glass-fiber filters to retain membrane-bound radioligand. Filters were washed 2 times with 5 ml of ice-cold buffer. Radioactivity remaining on the filters was counted by liquid scintillation spectroscopy. Samples were analyzed in triplicate.

Data Analysis

Nonlinear regression was used to determine the 50% inhibitory concentration (IC₅₀) for each displacement curve.¹¹ For muscarinic receptor subtypes results from three separate binding experiments are expressed as mean values ± SD for the (-)log IC₅₀. Comparisons of results for each receptor subtype were analyzed by analysis of variance and Neuman-Keuls multiple comparison test.

Materials

(±)-Chlorpheniramine maleate, terfenadine, and atropine were purchased from Sigma Chemical Co. (St. Louis, MO). (±)-Brompheniramine maleate was obtained from Whitehall-Robins Healthcare (Madison, NJ). Protein was determined by the Pierce BCA protein assay (Rockford, IL). [³H]-N-methyl-scopolamine (specific activity 82 Ci/mmol) was purchased from Amersham Corporation (Arlington Heights, IL).

Results

Table 1 is a summary of results of receptor-binding studies at the human muscarinic cholinergic receptor. Atropine was used as the standard and shows high affinity for all subtypes of the receptor. The H₁-receptor antagonists brompheniramine, chlorpheniramine, and terfenadine were significantly less potent than atropine ($p < 0.01$) at all subtypes. Atropine, brompheniramine, and chlorpheniramine could not discriminate between m1–m5. No significant difference was observed between chlorpheniramine and brompheniramine. Terfenadine's affinity was significantly less than atropine's, and significantly greater than brompheniramine's and chlorpheniramine's at m3 ($p < 0.01$). Terfenadine was 5 times more potent at m3 than at m4 ($p < 0.05$). Representative curves are shown in Figure 1.

Discussion

Clinical effects of classic antihistamines, including symptomatic treatment of the common cold, as well as adverse effects, including dry mouth, blurred vision, and urinary retention, are attributed to the drugs' affinities for muscarinic cholinergic receptors. As shown by data reported here, brompheniramine, chlorpheniramine, and terfenadine are approximately equivalent in their potencies at human m1–m5. Their affinities for these receptors are significantly less than that of atropine.

To our knowledge, this is the first evaluation of brompheniramine, chlorpheniramine, and terfenadine at the five subtypes of the human muscarinic cholinergic receptor. The availability of the cloned human receptor subtypes as a research tool is potentially important for comparison of in vitro affinities of antihistamines. Previous research evaluated the potencies of chlorpheniramine, brompheniramine, and terfenadine at the muscarinic cholinergic receptor in bovine cortex and rat brain.^{10, 12, 13} Those studies reported an 50% effective concentration (EC₅₀) of the three agents of approximately 20 μM ^{10, 13} for rat brain receptors. Affinities in the present study are in agreement. Although terfenadine is commonly described as lacking effects at muscarinic cholinergic receptors,⁵ compared with brompheniramine and chlorpheniramine it has equivalent or greater potency at the five human subtypes in vitro. Although a direct comparison between terfenadine and brompheniramine or chlorpheniramine must be tempered by the use of DMSO as a diluent for

terfenadine and not for the other drugs, our results are in agreement with those of in vitro studies.^{10, 13}

Knowledge of receptor subtype distribution could potentially be used to target specific receptors for selected effects. In rat peripheral tissues, subtype-selective antisera determined muscarinic receptor subtype distribution for m1, m2, and m3, and showed that m2 accounts for 70–90% of muscarinic receptors in bladder, lungs, and ileum, with m3 accounting for 5–11%.¹⁴ In contrast, rabbit lung contains m2 and m4 receptors.¹⁵

The m3 muscarinic cholinergic receptor mRNA was identified in epithelial cells, serous and mucous cells of submucosal glands, and

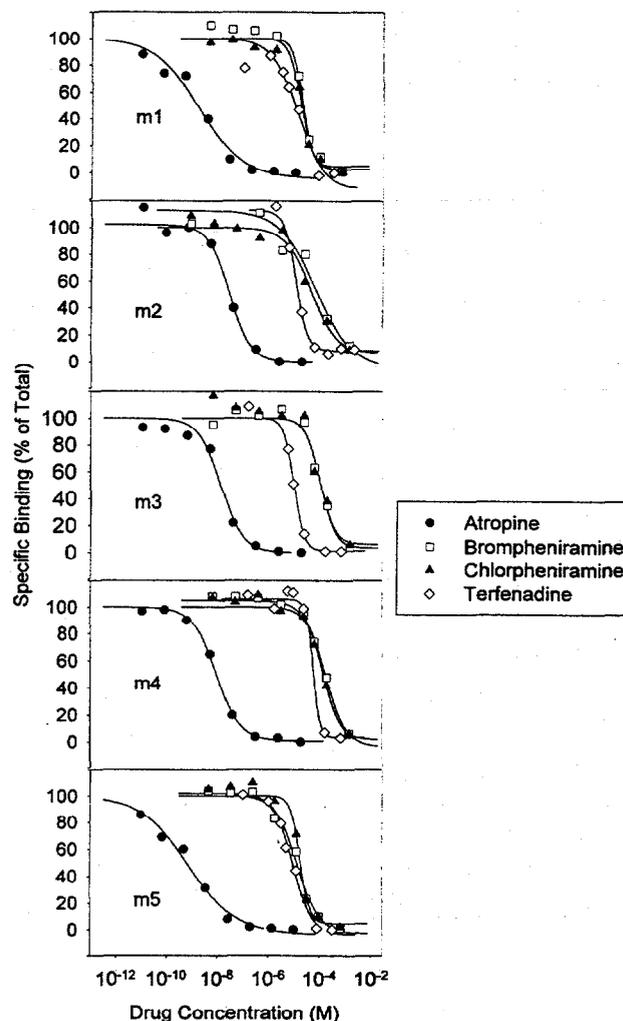


Figure 1. Displacement of [³H]-N-methyl-scopolamine binding to CHO cells stably transfected with the indicated muscarinic cholinergic receptor subtypes m1–m5 in the presence of atropine, brompheniramine, chlorpheniramine, or terfenadine. Representative curves are shown.

endothelial cells of human nasal mucosa.¹⁶ Nasal provocation studies showed the pharmacologically defined M1 and M3 receptors to be present and to regulate secretion of mucus glycoproteins in human nasal mucosa.¹⁷ Generally, these pharmacologically defined receptors (M1 and M3) correspond to m1 and m4, and m3, respectively.¹⁸ It is likely that activity at specific subtypes localized in various tissues accounts for therapeutic and adverse effects of antihistamines. For example, m1, m3, and m4 may be target receptors in human nasal mucosa for treating symptoms of allergic rhinitis or common cold. Other subtypes may be responsible for effects such as urinary retention in peripheral tissues such as the bladder. Characterization of any subtype selectivity of these drugs would be helpful in understanding their effects and in targeting specific receptors in new drug development.

We did not find human muscarinic cholinergic receptor subtype selectivity for brompheniramine or chlorpheniramine, nor did the two drugs appear pharmacologically different at any subtype. This is in agreement with an *in vitro* functional study in which no differences were observed between brompheniramine and chlorpheniramine in reducing methacholine-induced secretion from human nasal mucosa explants.¹⁹ Lack of subtype selectivity also was observed for cyproheptadine and diphenhydramine.^{20, 21}

Terfenadine, in contrast to first-generation antihistamines evaluated, has approximately 5-fold selectivity for human m3, as shown in the present study. Clinically, it does not have effects that could be attributed to the muscarinic cholinergic receptor. In humans, a single 60-mg dose of terfenadine had no effect on citric acid-stimulated salivary flow,²² mediated in part by cholinergic receptors,²³ whereas a single 8-mg dose of chlorpheniramine significantly reduced it.²² Oral terfenadine had no benefit in relieving symptoms of the common cold.²⁴ Lack of anticholinergic effect after oral administration is most likely due to rapid metabolism of the drug to its acid metabolite fexofenadine, allowing for little accumulation of parent compound. However, it is conceivable that if terfenadine were applied topically to nasal membranes, as is currently the method of delivery for some antihistamines, it would have a local anticholinergic effect in these tissues in which m3 receptors play a role in human nasal mucosal secretions.¹⁷

In summary, brompheniramine and chlorpheniramine did not discriminate between

human muscarinic cholinergic receptor subtypes and terfenadine showed selectivity for the human m3 receptor subtype. *In vitro* comparisons with human muscarinic receptor subtypes could help explain similarities or differences between clinically observed anticholinergic effects of antihistamines and could potentially target receptor-specific effects of such agents.

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- HOLD Weekday at FedEx Location Not available with FedEx First Overnight
- HOLD Saturday at FedEx Location Available for FedEx Priority Overnight and FedEx 2Day to select locations

Does this shipment contain dangerous goods?
 One box must be checked.
 No Yes As per attached Shipper's Declaration Yes Shipper's Declaration not required Dry Ice Dry Ice, 9 UN 1845 x kg Cargo Aircraft Only

7 Payment Bill to: Enter FedEx Acct. No. or Credit Card No. below.
 Sender Acct. No. in Section 1 will be billed. Recipient Third Party Credit Card Cash/Ch Obtain Recip. Acct. No.

Total Packages	Total Weight	Total C

8 Release Signature Sign to authorize delivery without obtaining signature.

By signing you authorize us to deliver this shipment without obtaining a signature and agree to indemnify and hold us harmless from any resulting claims.
 Questions? Call 1-800-Go-FedEx (800-463-3339)
 Visit our Web site at www.fedex.com
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RECIPIENT: PEEL HERE