

L12

ANNALS OF ALLERGY, ASTHMA, & IMMUNOLOGY

June, 1999
Volume 82, Number 6

WESTON LIBRARY
JUN 24 1999
J5/120 CLINICAL SCIENCES CENTER
600 HIGHLAND AV-MADISON, WI 53792

Guest Editorial

Physician Leadership in the New Millennium William E Berger, MD, MBA

Review Article

Antifungals in the Treatment of Allergic Bronchopulmonary Aspergillosis
Eddie E Leon, MS and Timothy J Craig, DO

Original Articles

A Six-Month, Placebo-Controlled Comparison of the Safety and Efficacy of Salmeterol or Beclomethasone for Persistent Asthma Robert A Nathan, MD; Jacob L Pinnas, MD; Howard J Schwartz, MD; Jay Grossman, MD; Steven W Yancey, MS; Amanda H Emmett, MS; and Kathleen A Rickard, MD

Asthma, Mite Sensitization, and Sleeping in Bunks Pere Gaig, MD; Ernesto Enrique, MD; Pilar García-Ortega, MD; Montserrat Olona, MD; María del Mar San Miguel, MD; and Cristobal Richart, MD

Double-Blind Trials of Azelastine Nasal Spray Monotherapy Versus Combination Therapy with Loratadine Tablets and Beclomethasone Nasal Spray in Patients with Seasonal Allergic Rhinitis William E Berger, MD, MBA; Stanley M Fineman, MD; Phillip Lieberman, MD; Robert M Miles, MD; and the Rhinitis Study Groups

A Summary of the Atmospheric Surveys Published in the United States Allergy Literature, 1966-1996 David A Frenz, Laura W Murray, and Adrienne A Boire

Prevention of Exercised-Induced Asthma by a Natural Isomer Mixture of β -Carotene Ittai Neuman, MD; Hermona Nahum, MSc; and Ami Ben-Amotz, PhD

Risk Factors for Acetaminophen and Nimesulide Intolerance in Patients with NSAID-Induced Skin Disorders Riccardo Asero, MD

Relationship Between Induced Sputum Cell Counts and Fluid-Phase Eosinophil Cationic Protein and Clinical or Physiologic Profiles in Mild Asthma V Gutiérrez, L Prieto, V Torres, R Trenor, C Pérez, J M Bertó, and J Marín

Immediate Hypersensitivity in Adults with IgG Deficiency and Recurrent Respiratory Infections Valentin Popa, MD and Stephen M Nagy, Jr, MD

Exercise-Induced Hyperventilation: a Pseudoasthma Syndrome Abdel-Hai Hammo, MD and Miles M Weinberger, MD

(Complete Table of Contents appears on page A-2)

Next Annual Meeting: November 12-17, 1999, Chicago, Illinois

Official Publication of the American College of Allergy, Asthma & Immunology

ANNALS OF ALLERGY, ASTHMA, & IMMUNOLOGY

Formerly published as ANNALS OF ALLERGY
Contents of ANNALS OF ALLERGY, ASTHMA, & IMMUNOLOGY Copyright © 1999 by the American College of Allergy, Asthma, & Immunology.

Editor: Edward J O'Connell, MD
Mayo Clinic
411 Guggenheim Bldg
200 First St SW
Rochester, MN 55905
507-538-0009

The Annals of Allergy, Asthma, & Immunology is the Official Publication of the American College of Allergy, Asthma, & Immunology. It is published monthly by the American College of Allergy, Asthma, & Immunology

June, 1999

GUEST EDITORIAL

Physician Leadership in the New Millennium William E Berger, MD, MBA..... 507

REVIEW ARTICLE

Antifungals in the Treatment of Allergic Bronchopulmonary Aspergillosis Eddie E Leon, MS and Timothy J Craig, DO..... 511

ORIGINAL ARTICLES

A Six-Month, Placebo-Controlled Comparison of the Safety and Efficacy of Salmeterol or Beclomethasone for Persistent Asthma Robert A Nathan, MD; Jacob L Pinnas, MD; Howard J Schwartz, MD; Jay Grossman, MD; Steven W Yancey, MS; Amanda H Emmett, MS; and Kathleen A Rickard, MD 521

Asthma, Mite Sensitization, and Sleeping in Bunks Pere Gaig, MD; Ernesto Enrique, MD; Pilar García-Ortega, MD; Montserrat Olona, MD; María del Mar San Miguel, MD; and Cristobal Richart, MD..... 531

Double-Blind Trials of Azelastine Nasal Spray Monotherapy Versus Combination Therapy with Loratadine Tablets and Beclomethasone Nasal Spray in Patients with Seasonal Allergic Rhinitis William E Berger, MD, MBA; Stanley M Fineman, MD; Phillip Lieberman, MD; Robert M Miles, MD; and the Rhinitis Study Groups 535

A Summary of the Atmospheric Surveys Published in the United States Allergy Literature, 1966-1996 David A Frenz, Laura W Murray, and Adrienne A Boire 543

Prevention of Exercise-Induced Asthma by a Natural Isomer Mixture of β -Carotene Ittai Neuman, MD; Hermona Nahum, MSc; and Ami Ben-Amotz, PhD 549

(Continued on page A-4)

For submission of articles, see "Instructions for Authors"
Changes of address directed to the ANNALS OF ALLERGY, ASTHMA, & IMMUNOLOGY should be sent to:
Jim Slawny, Executive Director
ANNALS OF ALLERGY, ASTHMA, & IMMUNOLOGY
Suite 550, 85 West Algonquin Road, Arlington Heights Illinois 60005
Telephone - (847) 427-1200
email: annallergy@his.com

Annals of Allergy, Asthma, & Immunology (ISSN-1081-1206) is published monthly for \$50.00 (US), \$75.00 (US institutions) and \$78.00 (foreign) by the American College of Allergy, Asthma, & Immunology, 7212 Davis Ct, McLean, VA 22101. Periodicals postage paid at McLean, VA and additional mailing offices. (POSTMASTER: Send address changes to AMERICAN COLLEGE OF ALLERGY, ASTHMA, & IMMUNOLOGY, 85 West Algonquin Road, Suite 550, Arlington Heights, IL 60005.) Printed in the USA.

(Continued from page A-2)

Risk Factors for Acetaminophen and Nimesulide Intolerance in Patients with NSAID-Induced Skin Disorders Riccardo Asero, MD	554
Relationship Between Induced Sputum Cell Counts and Fluid-Phase Eosinophil Cationic Protein and Clinical or Physiologic Profiles in Mild Asthma V Gutiérrez, L Prieto, V Torres, R Trenor, C Pérez, J M Bertó, and J Marín	559
Immediate Hypersensitivity in Adults with IgG Deficiency and Recurrent Respiratory Infections Valentin Popa, MD and Stephen M Nagy, Jr, MD	567
Exercise-Induced Hyperventilation: a Pseudoasthma Syndrome Abdel-Hai Hammo, MD and Miles M Weinberger, MD	574
Expression of ICAM-1 on Conjunctival Epithelium and ECP in Tears and Serum from Children with Allergic Conjunctivitis Jae-Won Oh, MD; Jung-Chul Shin, MD; Se-Jin Jang, MD; and Ha-Baik Lee, MD	579
Differences of Genetic Effects for the Development of Allergic Diseases in Two Cities of Japan Hiroatsu Agata, MD; Norito Kawakami, MD; Naomi Kondo, MD; Terue Hayashi, MD; Osamu Fukutomi, MD; Hiroyuki Shimizu, MD; and Tadao Orii, MD	586
<hr/>	
Author Index to Abstracts Presented at the 55th Annual Meeting of the ACAAI, Philadelphia, Pennsylvania	592
<hr/>	
Author Index to Volume 82, 1998	598
<hr/>	
CME EXAMINATION	516
CME EXAMINATION ANSWERS (Identification No 009-005)	518
CME EXAMINATION ANSWER SHEET	519
INSTRUCTIONS FOR AUTHORS	A-7
CLASSIFIED ADVERTISING	530, 534, 542
ERRATA	542
LETTER TO THE EDITOR	
Possible Mechanism of Paracetamol Anaphylaxis	591

Double-blind trials of azelastine nasal spray monotherapy versus combination therapy with loratadine tablets and beclomethasone nasal spray in patients with seasonal allergic rhinitis

William E Berger, MD, MBA*, Stanley M Fineman, MD†, Phillip Lieberman, MD‡, Robert M Miles, MD§; and the Rhinitis Study Groups¶

Background: Azelastine hydrochloride is an H₁-receptor antagonist with anti-inflammatory properties that is available in the US as Astelin Nasal Spray for the treatment of seasonal allergic rhinitis. The symptoms of seasonal allergic rhinitis can initially be treated with monotherapy using either an antihistamine or an intranasal corticosteroid. Patients whose symptoms do not respond adequately are often prescribed a combination of both an antihistamine and an intranasal corticosteroid.

Objective: Three multicenter, randomized, double-blind studies were conducted to determine whether patients with moderate-to-severe symptoms of seasonal allergic rhinitis who had responded inadequately to monotherapy with either an oral antihistamine or an intranasal corticosteroid, and who were candidates for combination therapy with both an oral antihistamine and an intranasal corticosteroid, could be effectively treated with azelastine nasal spray monotherapy.

Methods: Following a 1- to 2-week washout period, patients were randomized to 7 days of double-blind treatment with either azelastine nasal spray (2 sprays per nostril bid, 1.1 mg/day) monotherapy or combination therapy with oral loratadine (Claritin, one 10-mg tablet/day) plus intranasal beclomethasone dipropionate monohydrate (Beconase AQ, 2 sprays per nostril bid, 336 µg/day). Efficacy was determined at the end of the study by both a physician assessment of the need for additional anti-rhinitis medication and a patient global evaluation of therapeutic effectiveness. The three studies were conducted at 71 investigational sites during the 1998 spring allergy season. Three separate studies were conducted to verify the reproducibility of the new study design.

Results: In all three studies a total of 1,070 patients were randomized to double-blind treatment. There were no statistically significant differences in the percentage of patients treated with azelastine nasal spray versus patients treated with a combination of loratadine tablets and beclomethasone nasal spray who did not require additional anti-rhinitis medication (32% to 45% and 39% to 46%, respectively). The patient global evaluation indicated that 77% to 84% of the patients treated with azelastine nasal spray had symptomatic improvement and 85% to 90% of the patients treated with loratadine tablets and beclomethasone nasal spray had symptomatic improvement. The most commonly reported adverse experience with azelastine nasal spray was a transient aftertaste (8%), while the most commonly reported adverse experience with loratadine tablets and beclomethasone nasal spray in combination was headache (6%).

Conclusions: Based on the percentage of patients not requiring additional anti-rhinitis medication and the patient assessment of efficacy, azelastine nasal spray monotherapy was as effective as the combination of oral loratadine plus intranasal beclomethasone in treating moderate-to-severe symptoms of seasonal allergic rhinitis.

Ann Allergy Asthma Immunol 1999;82:535-541.

INTRODUCTION

Azelastine hydrochloride, a phthalazine derivative, is a high-affinity his-

tamine H₁-receptor antagonist¹ administered as a nasal spray for the treatment of seasonal allergic rhinitis.

In addition to H₁-receptor antagonism, azelastine also affects cells and chemical mediators of the inflammatory response as shown in *in vitro* studies²⁻⁷ and in animal models of allergic inflammation.⁸⁻¹⁰ In clinical trials in patients with seasonal allergic rhinitis, azelastine reduced levels of leukotrienes and kinins following nasal allergen challenge¹¹ and downregulated intercellular adhesion molecule-1 (ICAM-1) expression while reducing eosinophil and neutrophil infiltration in both the early- and late-phase of the allergic response.¹²

* Southern California Research Center, 26732 Crown Valley Parkway, Suite 361, Mission Viejo, California and Allergy and Asthma Associates, 27800 Medical Center, Suite 150, Mission Viejo, California; † Atlanta Allergy and Immunology Research Foundation, 790 Church, Suite 410, Marietta, Georgia; ‡ 300 Walnut Bend Road South, Cordova, Tennessee; § 1715 Thomson Drive, Lynchburg, Virginia. ¶ The members of the Rhinitis Study Groups are as follows: Study No. 1—J. Spencer Atwater Jr, Asheville, NC; James Baker, Portland, OR; Charles Banov, Charleston, SC; William Berger, Mission Viejo, CA; Robert Berkowitz, Atlanta, GA; David Bernstein, Cincinnati, OH; Don Bukstein, Madison, WI; Jim Christensen, Las Vegas, NV; David Cook, Walnut Creek, CA; Jonathan Corren, Los Angeles, CA; Peter Creticos, Baltimore, MD; Ira Finegold, New York, NY; Stanley Fineman, Atlanta, GA; Stanley Galant, Orange, CA; Sherwin Gillman, Orange, CA; Elliot Ginchansky, Dallas, TX; Pinkus Goldberg, Indianapolis, IN; Alan Goldsobel, San Jose, CA; Gary Gross, Dallas, TX; Philip Halverson, Minneapolis, MN; Paul Hannaway, Salem, MA; Melvin Haysman, Savannah, GA; Lewis Kanter, Camarillo, CA. Study No. 2—William Berger, Mission Viejo, CA; Richard Collins, Charlotte, NC; Thomas Flaim, Albany, NY; David Gosage, Knoxville, TN; Frederic Kiechel, Lincoln, NE; Craig LaForce, Raleigh, NC; Bobby Lanier,

In United States clinical trials,¹³⁻¹⁷ azelastine nasal spray, at a dosage of 2 sprays per nostril bid (1.1 mg/day), was effective in the management of a complex of symptoms associated with seasonal allergic rhinitis, including rhinorrhea, sneezing, nasal pruritus, post-nasal drip, and itchy and watery eyes. Many patients with nasal congestion also experienced improvement in this symptom, an effect not typically associated with oral antihistamines. Onset and duration of action assessments^{13,14} showed that azelastine nasal spray improved baseline symptom scores within 1 to 3 hours, while other studies¹⁸ suggested that improvements may be evident in less than 30 minutes in some patients. Transient aftertaste, headache, somnolence, and nasal burning were the most commonly reported adverse experiences with azelastine nasal spray, and there have been no serious

Ft Worth, TX; Dennis Ledford, Tampa, FL; William Lumry, Dallas, TX; Lyndon Mansfield, El Paso, TX; Jonathan Matz, Baltimore, MD; Donald McNeil, Worthington, OH; J Allen Meadows, Montgomery, AL; Robert Miles, Lynchburg, VA; David Miller, North Dartmouth, MA; Don Mitchell, Jackson, MS; William Morgan, Glendale, AZ; Zev Munk, Houston, TX; Martin Murcek, Greensburg, PA; Harold Nelson, Denver, CO; Thomas Nilsson, Omaha, NE; Michael Noonan, Portland, OR; Andrew Pedinoff, Princeton, NJ; William Storms, Colorado Springs, CO. Study No. 3—Jeffrey Adelglass, Dallas, TX; William Berger, Mission Viejo, CA; Fred Grogan, Cordova, TN; Hobert Pence, Louisville, KY; Jacob Pinna, Tucson, AZ; Bruce Prenner, San Diego, CA; Paul Ratner, San Antonio, TX; Robert Reisman, Williamsville, NY; Thomas Rosenberg, Wichita, KS; Eric Schenkel, Easton, PA; William Schoenwetter, Minneapolis, MN; Eugene Schwartz, Altamont Springs, FL; Nathan Segall, Atlanta, GA; Jay Selcow, Hartford, CT; Martin Sher, Largo, FL; Charles Siegel, Gladstone, MO; William Silvers, Englewood, CO; Mark Stein, North Palm Beach, FL; Stanislaus Ting, Las Cruces, NM; Ned Whitcomb, Carmichael, CA; John Winder, Sylvania, OH; Thomas Woehler, Houston, TX; Barry Zeffren, Glen Carbon, IL; Myron Zitt, North Babylon, NY.

This research was funded by a grant from Wallace Laboratories, Division of Carter-Wallace, Inc., Half Acre Road, Cranbury, New Jersey.

Received for publication January 4, 1999.

Accepted for publication in revised form March 30, 1999.

adverse experiences associated with its use.

An antihistamine alone or a nasal corticosteroid alone can be used as first-line therapy for the treatment of seasonal allergic rhinitis, and for those patients whose symptoms are not adequately controlled by either treatment often a combination of both an antihistamine with an intranasal corticosteroid is prescribed. Three multicenter, randomized, double-blind, parallel-group studies were conducted to compare the effectiveness of azelastine nasal spray monotherapy versus combination therapy with beclomethasone nasal spray plus loratadine tablets in patients with moderate-to-severe symptoms of seasonal allergic rhinitis who had not adequately responded to monotherapy with either a nasal steroid or an oral antihistamine and who would be considered candidates for combination therapy with a nasal steroid and an oral antihistamine. Efficacy was evaluated by (1) comparing the percentage of patients in each treatment group not requiring additional anti-rhinitis therapy based on a physician assessment at the end of the double-blind treatment period and (2) comparing the percentage of patients with symptomatic improvement in each treatment group based on a patient global rating of therapeutic effectiveness.

METHODS

Patients

All patients were 12 years of age or older with a documented history of seasonal allergic rhinitis. Each patient was currently being treated with a monotherapy regimen, either an oral antihistamine or a nasal steroid, and was considered by the investigator to be a candidate for combination therapy with an oral antihistamine plus a nasal steroid due to lack of adequate symptom control. Female patients were non-gravid, non-nursing, of non-childbearing potential or, if of childbearing potential agreed not to become pregnant during the study. Sexually active females of childbearing potential were

practicing an adequate method of birth control. Patients unable to use or tolerate nasal spray, patients with asthma, patients who were treated with any investigational drug within 30 days of enrollment into this study, and patients being treated with antidepressant drugs were excluded from participation. Patients were also excluded if they had an acute respiratory infection within 30 days of the study or any clinically significant acute or chronic illness. All patients signed a written informed consent document before entering the study, and written consent of a parent or legal guardian was required for patients under the legal age of consent.

Study Design

The three studies were carried out during the 1998 spring allergy season at 71 investigational sites distributed throughout the contiguous United States. These studies were randomized, double-blind, parallel-group trials consisting of 1- to 2-week baseline washout period (1 week for patients being treated with an oral antihistamine and 2 weeks for patients being treated with an intranasal steroid) followed by a 7-day double-blind treatment period. Chlorpheniramine maleate (Chlor-Trimeton Tablets 4 mg) was permitted on an "as needed" basis for the treatment of seasonal allergic rhinitis symptoms during the baseline washout period; however, it was not permitted for 48 hours before the patients were randomized to double-blind treatment.

After the baseline washout period and prior to randomization, a physician assessment was made of the severity of rhinitis symptoms, including nose blows, sneezes, runny nose/sniffles, itchy nose, watery eyes, itchy eyes/ears, itchy throat/palate, cough, post-nasal drip, and nasal congestion. Patients who qualified for randomization to double-blind treatment had symptom rating scores of at least 18 (scale = 0 to 50) with at least three of the symptoms of moderate or greater than moderate intensity. For nose blows and sneezes, the actual number of each per day were counted and scored according to the following

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.