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ORIGINAL RESEARCH—ALLERGY

An assessment of the onset and duration of action of olopatadine nasal spray

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OBJECTIVE: Seasonal allergic rhinitis (SAR) is a highly prevalent disease. This study was conducted to evaluate the onset and duration of action of three concentrations of olopatadine nasal spray.

METHODS: This was a randomized, double-blind, single-dose, placebo-controlled study, conducted in an environmental exposure chamber in patients with SAR. A total of 320 patients were exposed to ragweed allergen in the chamber and randomized to olopatadine nasal spray 0.2%, 0.4%, 0.6%, or placebo nasal spray. Symptoms (sneezing, runny, itchy, and stuffy nose) were self-assessed during a 12-hour study period.

RESULTS: All concentrations of olopatadine nasal spray provided clinically meaningful reductions in total nasal symptom scores at 30 minutes compared to the placebo. Olopatadine nasal spray 0.6% was significantly more effective ($P < 0.05$) than placebo nasal spray at all time-points starting at 90 minutes post-dose and continuing over 12 hours.

CONCLUSIONS: Olopatadine nasal spray 0.6% demonstrated a fast onset of action and maintained an effect for at least 12 hours after dosing.

Seasonal allergic rhinitis (SAR) is a highly prevalent disease that results in considerable health-related and economic cost.[1] Allergic rhinitis is characterized by symptoms of runny nose, nasal itching, nasal congestion, and sneezing, but may also be associated with other symptoms such as postnasal drip, ocular itching or redness, ear fullness or itching, or headache.[1,2] Rapid onset of symptom relief and effective control of the signs and symptoms associated with allergic rhinitis should be primary goals of treatment. In a survey of 1033 patients with allergic rhinitis, 85% of patients indicated that a medication that works quickly to relieve symptoms was important.[3]

Olopatadine HCl is a unique antiallergy drug with more than one mechanism of action. It acts as a selective H1 histamine receptor antagonist and also inhibits the release of histamine and other proinflammatory mediators from human mast cells.[4] Administering antihistamines topically has the advantage of delivering a high concentration of drug to the target organ while minimizing systemic side effects. An ophthalmic formulation of olopatadine (Patanol [olopatadine HCl 0.1%] ophthalmic solution in the United States, Opatanol in Europe) is indicated for the treatment of the signs and symptoms of allergic conjunctivitis. In clinical studies, ophthalmic olopatadine is well tolerated and has shown a rapid onset of action.[5] An intranasal formulation of olopatadine hydrochloride is now under development for the prevention and treatment of SAR.

The present study was a randomized, double-blind, placebo-controlled study conducted in an environmental exposure chamber (EEC). The purpose of the study was to evaluate the onset and duration of action of three concentrations of olopatadine nasal spray on allergic rhinitis symptoms.

METHODS

Overall Study Design

This study was a single-center (Mississauga, Ontario, Canada), controlled-exposure, randomized, double-masked, vehicle-controlled, parallel group comparison of three concentrations of olopatadine nasal spray (0.2%, 0.4%, 0.6%) compared with a placebo nasal spray (olopatadine HCl nasal spray vehicle) in an EEC. The study was divided into three sessions as illustrated in Figure 1. This included a screening visit, two or more priming visits, and a treatment visit. Successfully "primed" patients who met all inclusion/exclusion criteria were randomized to receive either olopatadine 0.2%, 0.4%, 0.6%, or a placebo nasal spray on the 1-day treatment visit and evaluated for 12 hours after dosing. This study was performed in compliance with the ethical principle of the Declaration of Helsinki and Good Clinical Prac-

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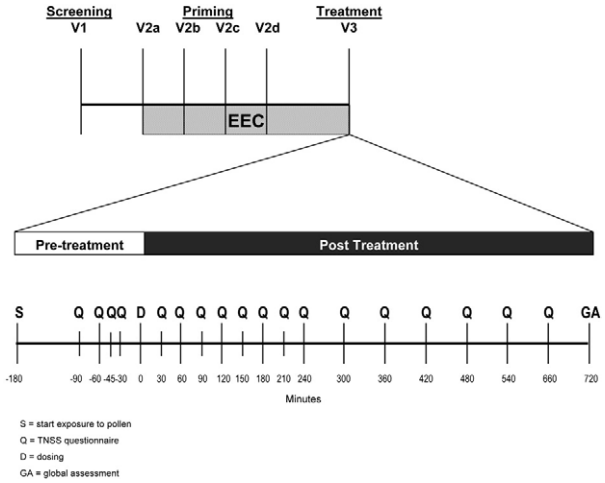

Figure 1 Study design.

tices (GCP). Protocol and informed consent were approved by IRB Services (Aurora, Ontario, Canada). The first patient was enrolled in May 2002, and the last patient exited in July 2002.

Study Population

Patients 17 to 65 years old with a history of nonrecalcitrant SAR during the fall allergy season and allergy to short ragweed pollen (defined as a positive case history and skin prick or intradermal test) within 12 months before screening were considered for participation. Women of child-bearing potential were allowed in the study if they had a negative pregnancy test before randomization and agreed to use adequate birth control methods during the study.

Patient exclusion criteria were the use or inadequate wash-out of study-prohibited drug; known nonresponder to antihistamines; any significant nasal abnormalities; nasolacrimal drainage system malfunction; any significant disease of any major organ, such as a history of severe or uncontrolled cardiovascular, hepatic, or renal disease; acute or significant chronic sinusitis; upper respiratory tract infection or asthma (except mild intermittent asthma); hypersensitivity to any component of the investigational treatment; history of drug or alcohol abuse in the past 10 years; pregnancy; or participation in any other investigation or treatment with any investigational drug within 30 days before entry or during the study.

Excluded medications were antibiotics, antihistamines, leukotriene inhibitors, corticosteroids, immunotherapies, ipatropium bromide, atropine, nedocromil/cromolyn, topical nasal or oral decongestants, or monoamine oxidase inhibitors within a time period based on their pharmacology before the first priming visit. Other drugs were permitted only if they were not expected to interfere with the ability of the patient to participate in the study. The use of alcohol within 24 hours of the each visit was prohibited.

Outcome Measures

The severity of allergic rhinitis symptoms (sneezing, runny, itchy, and stuffy nose) were recorded by the patient on machine-readable diary cards with the following 4 point scale: 0, absent symptoms; 1, mild symptoms; 2, moderate symptoms; 3, severe symptoms.[6] The total nasal symptom score (TNSS) was calculated as the sum of the individual severity scores for each of the four symptoms at the individual time-points. The average of the -30 and -45 predose TNSS values at the treatment visit (before receiving study medication) was used as baseline for each treatment group. The primary clinical efficacy variable under analysis for each treatment was change from baseline in TNSS.

Patients also completed the Patient Global Rating Scale that rated their responses on a 7-unit scale. The Patient Global Rating Scale asked the patient, "since taking my dose of study medication, I would rate my overall allergy symptoms throughout the day as . . ." 0, very much better; 1, moderately better; 2, a little better; 3, unchanged; 4, a little worse; 5, moderately worse; 6, very much worse.

Priming Visit

Patients who met all inclusion/exclusion criteria were scheduled to return in less than two weeks for the priming visits. During priming, patients were exposed to ragweed pollen for three hours in one or more priming sessions in the environmental exposure chamber (EEC). Patients were instructed to record their instantaneous (how they felt at the time of assessment) SAR symptoms on diary cards at 30-minute intervals. Patients were required to achieve a TNSS of at least 6 out of 12 on a total of two priming visits to be considered "primed." All primed patients were eligible to return for the treatment phase.

Treatment Visits

Eligible patients returned for the single day treatment visit. All patients arrived at the study site, and their medication and health history were reviewed, including a pregnancy test (if applicable). At 7:00 AM patients entered the EEC and were exposed to pollen for 14.5 hours (2.5 hours predose and 12 hours postdose of test article). Patients rated their pretreatment symptoms at −1.5 hour, −1.0 hour, −0.75 hour, and −0.5 hour before receiving study medication. Patients had to achieve a TNSS of at least 6 out of 12 (including a score of at least 2 for runny nose) on any one of four qualifying diary cards to receive treatment. Patients who failed to meet the minimum qualifying score were discontinued from the study. In addition, patients assessed with unilateral or bilateral complete nasal blockage after the fourth qualifying diary card were discontinued from the study.

All qualified and eligible patients were enrolled into the study with the list of patient numbers provided by Alcon Biostatistics. Patients were enrolled sequentially as they qualified. The numeric series of patient numbers contained a built-in randomization scheme to ensure that patients were