EXHIBIT 36

The New Topical Steroid Ciclesonide Is Effective in the Treatment of Allergic Rhinitis

Bernhard M. W. Schmidt, MD, Wolfgang Timmer, MD, Anette C. Georgens, Monika Hilt, Catherine Mattinger, MD, Wilhelm Wurst, MD, Karl Hörmann, MD, and Martin Wehling, MD

A randomized, placebo-controlled, double-blind crossover study was performed to investigate the efficacy of ciclesonide nasal spray in allergic rhinitis at the dose level of 200 µg per nostril. Twenty-four subjects (13 males, 11 females; median age: 28 years) with a history of allergic rhinitis but free of symptoms at screening entered the study. Ciclesonide and placebo were given for 7 days each with a washout period of at least 14 days in between. In both treatment periods, controlled intranasal allergen provocation with pollen extracts was performed on the 2 days before start of treatment (days −2 and −1) and on all treatment days (days 1 to 7) about 2 hours after administration of the study medication. At 5 and 30 minutes after each allergen provocation, rhinal airflow was measured by anterior rhinomanometry, and the subjective symptoms of obstruction, itching, and rhinorrhea were assessed by means of a standardized visual analog scale. Rhinal airflow improved significantly from day 5, while the subjective symptom of obstruction improved from day 2. Itching and rhinorrhea also improved significantly. The local and systemic tolerability of ciclesonide nasal spray was excellent. The results of this study clearly indicate that the new topical steroid ciclesonide is effective in the treatment of allergic rhinitis without producing local or systemic side effects.

Journal of Clinical Pharmacology, 1999;39:1062-1069

Allergic rhinitis is a common disease that is characterized by nasal obstruction, itching, rhinorrhea, and eye symptoms. Allergic rhinitis can occur seasonally and in a perennial form. Seasonal allergic rhinitis is triggered mainly by natural pollen exposure, while perennial allergic rhinitis may be caused by various environmental allergens. After exposure to a specific antigen, mediators such as prostaglandin D2, leukotriene E4, tryptase, and histamine are released during an early allergic reaction, which causes sneezing, nasal blockage, and rhinorrhea. After improvement of symptoms, a late-phase reaction may typically occur between 3.5 and 8.5 hours after allergen provocation.[1] Allergic inflammation in the nose is mainly due to recruitment of eosinophils and metachromatic cells.[2] Human allergen-induced responses in the nose are used as a suitable model for allergic inflammation.[3,4]

Allergic rhinitis affects 8% to 24% of the population in the industrialized countries.[5,6] In patients suffering from allergic rhinitis, the health-related quality of life is frequently impaired. When complete allergen avoidance is impossible, pharmacotherapy should be initiated. The International Rhinitis Management Group recommends a symptom-guided approach to the pharmacotherapy of allergic rhinitis.[7] Topical intranasal steroids provide rapid relief of symptoms of seasonal allergic rhinitis with minimal side effects. Therefore, they are considered first-line treatment for this disease. Immunotherapy is only recommended when pharmacotherapy does not lead to satisfactory relief of symptoms.[7,8]

From the Institute of Clinical Pharmacology, Mannheim University Hospital, Ruprecht-Karls-University Heidelberg, Mannheim, Germany (Dr. Schmidt, Ms. Georgens, Prof. Wehling); Byk Gulden Pharmaceuticals, Konstanz, Germany (Dr. Timmer, Ms. Hilt, Dr. Wurst); and the Department of Otorhinolaryngology, Mannheim University Hospital, Ruprecht-Karls-University Heidelberg, Mannheim, Germany (Dr. Mattinger, Prof. Hörmann). Submitted for publication December 14, 1998; revised version accepted May 25, 1999. Address for reprints: Prof. Martin Wehling, Head of the Institute of Clinical Pharmacology, Mannheim University Hospital, Faculty of Clinical Medicine Mannheim, Ruprecht-Karls-University Heidelberg, Theodor-Kutzer-Ufer 1-3, D-68167 Mannheim, Germany.

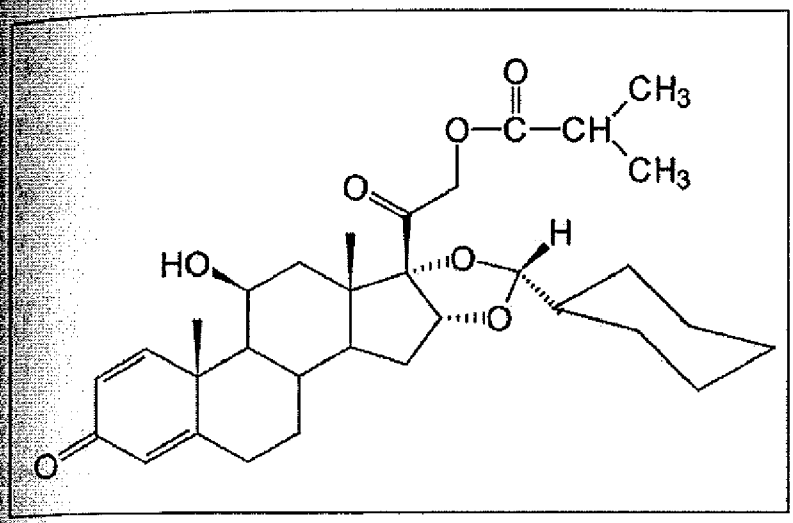

Figure 1. Structural formula of ciclesonide.

Ciclesonide is a new steroid under clinical development. The ciclesonide molecule has a chiral center in the acetal side chain. The two epimers of the compound are clearly different in their receptor affinities and metabolization rates. The R-epimer of ciclesonide (Figure 1) has a considerably higher binding affinity to the glucocorticoid receptor as compared to the S-epimer, and therefore only R-ciclesonide is developed for clinical use. This separation of epimers can be regarded as an essential progress in the development of topical steroids. In vivo, ciclesonide represents a prodrug that is cleaved locally to achieve topical effects.

The safety and tolerability of ciclesonide have been examined in a variety of preclinical tests investigating acute and chronic toxicity in different species. The anti-inflammatory potency of ciclesonide has been shown in various functional in vitro studies (e.g., inhibition of concanavalin A–induced proliferation of rat spleen cells) and in various preclinical in vivo inflammation models such as the rat cotton pellet test. Ciclesonide was very well tolerated when administered to healthy subjects in clinical phase I studies, and suppression of the endogenous cortisol release was minimal.

From the preclinical findings, it was presumed that administration of ciclesonide shows high local efficacy in patients with allergic rhinitis while systemic side effects are minimized. Therefore, the present study investigated whether intranasal administration of ciclesonide attenuates the symptoms of allergic rhinitis as compared to placebo. Secondary objectives were safety and local tolerability.

From the safety and efficacy evaluations of preclinical tests, it was concluded that 200 mg ciclesonide per nostril would be a reasonable dosage for intranasal administration in subjects with allergic rhinitis.

METHODS

Overall Study Design

The study was conducted as a randomized, placebo-controlled, double-blind, two-period crossover trial. Ciclesonide and placebo were given for 7 days each. Both treatment periods were separated by a washout period of at least 14 days. Controlled intranasal allergen provocation with commercially available pollen extracts was performed on the 2 days before the start of the respective treatment periods (study days –2 and –1) and on all treatment days (study days 1 to 7) about 2 hours after administration of the study medication. At 5 minutes and 30 minutes after the allergen challenge, the rhinal airflow was measured by rhinomanometry, and the subjective symptoms of obstruction, itching, and rhinorrhea were assessed by means of a standardized visual analog scale as described below. The two different assessment time points were chosen because of the known variability in the time courses of the patients' response to the allergen challenge.

Subjects

Twenty-four subjects (13 males, 11 females) with a history of allergic pollen rhinitis but free of symptoms at screening entered the study and were randomly

allocated to the two treatment sequences (ciclesonide/placebo, placebo/ciclesonide), which comprised 12 subjects each. The median age of the study participants was 28 years, and their median body weight was 76 kg.

Inclusion criteria were the following: history of seasonal allergic rhinitis, positive skin prick test, reduction of mean rhinal airflow after allergen provocation by at least 25% measured by rhinomanometry, and age between 18 and 45 years. Exclusion criteria were the following: any active disease or relevant abnormalities as ascertained in a prestudy examination, abnormal ENT (ear, nose, and throat) status (e.g., relevant septum deviation), symptoms of allergic rhinitis at screening, history of asthma attacks or severe anaphylactic reactions, any history of drug allergy, any medication no more than 2 weeks before the start of the study, and topical or systemic antiallergic medication, including steroids or decongestive nose drops no more than 4 weeks before the study. Subjects were not allowed to smoke more than 10 cigarettes per day or to drink alcohol or coffee excessively. In addition, the following exclusion criteria were taken into account for women: no reliable contraception in the cycle before the study, during the study period, and the cycle after the study (only IUD or registered hormonal contraceptives were allowed); pregnancy; or lactation period.

Screening Procedure and Allergen Provocation

All subjects underwent a comprehensive medical examination no more than 2 weeks prior to inclusion into the study. This screening examination comprised medical history and physical examination, including nose and throat, 12-lead ECG, body temperature, clinical laboratory parameters, and a skin prick test using a standard battery of 20 common aeroallergens. Only in case of positive skin prick test was a rhinomanometry carried out to obtain a baseline rhinal flow value, and immediately afterward controlled antigen delivery with commercially available pollen extracts (Allergopharma Joachim Ganzer KG, Reinbek, Germany) was performed by spraying two puffs of the pollen suspension in each nostril. The pollen extracts were prepared individually for each subject by choosing the one or two allergens that had evoked a major reaction in the skin prick test during the screening examination. For a particular subject, the same kind of allergen was used during the whole study. Nasal congestion was objectively assessed by standardized rhinomanometry using commercially available equipment (manufacturer: Allergopharma Joachim Ganzer KG, Reinbek, Germany). The right nostril was generally tested before the left one. Rhinal airflow was determined as the sum of both values obtained at a pressure difference of 150 Pa. The rhinal flow values at 5 and 30 minutes after the allergen provocation were averaged prior to further analysis. The percentage fall between the predose value (i.e., the resulting value for both nostrils) and the averaged value after allergen provocation served as inclusion criterion. A subject was only included into the study if the rhinal flow decreased by at least 25% after allergen provocation at screening. In case a particular allergen that had produced a major reaction in the prick test failed to cause a nasal reaction, and if the result of the skin prick test had shown multiple sensitivity, the nasal provocation test could have been repeated with another allergen that had caused a major skin reaction in the prick test.

Study Medication

Ciclesonide was administered using pressurized metered dose inhalers (MDI) with an attached nasal adapter. Each puff of released aerosol contained 200 µg ciclesonide. Placebo was administered using a device of identical appearance to facilitate the double-blind conduct of the study.

No concomitant medication was allowed during the study, except for the treatment of severe headache for which a limited amount of paracetamol (up to 1 g per day) might be taken.

Course of the Study

In each treatment period, the study medication was administered for 7 consecutive days (study days 1 to 7) at about 8:00 a.m. in the presence of the investigator. One puff of aerosol containing 200 µg ciclesonide or placebo was given into each nostril. The subjects had to breathe in continuously while the puff was released. Controlled antigen delivery was performed at 10:00 a.m. for 9 consecutive days (study days –2 to 7) in each study period by spraying two puffs of the pollen suspension into each nostril. At 5 and 30 minutes after each allergen provocation, subjective nasal symptoms (obstruction, itching, rhinorrhea) were evaluated, and rhinomanometric measurements were performed.

The three subjective symptoms were assessed by means of a standardized visual analog scale. An adequate position had to be marked by the subjects on a line between the two limits "not in existence" and "very strong." The length of the line was 10 cm, and a score number (value between 0 and 10) was ascertained by measuring the distance in cm from the beginning of

the line (position "not in existence") to the position marked. At each measuring time point, the assessment of the subjective findings, which comprised both nostrils, was implemented prior to the rhinomanometric measurements because the local manipulation might have temporarily influenced the outcome of nasal symptoms.

Safety and local tolerability of ciclesonide were assessed by continuous recording of adverse events and by safety measurements at final check. The poststudy examination, including an ENT check, was performed no more than 2 weeks after the end of the clinical part of the study.

The volunteers visited the study site at about 9:45 a.m. on study days –2 and –1 and at about 7:45 a.m. on study days 1 to 7 in both treatment periods. The study was conducted under controlled conditions. A physician was on duty during the entire study course. Before the subjects left the ward at about 11:00 a.m., the state of good health was confirmed by the responsible investigator.

Biostatistical Methods

The primary variable for confirmative biostatistical analysis was the rhinal airflow determined by rhinomanometry. To establish comparability of the pretreatment values, 90% confidence limits for the ciclesonide/placebo ratios of population medians were compared with conventional equivalence acceptance limits of 0.80 to 1.25[9,10] on days –2 and –1. On treatment days 1 to 7, the comparison of the rhinal airflow was done by means of the analysis of variance (ANOVA) for the two-treatment, two-period crossover design after logarithmic transformation. Geometric means and two-sided 95% confidence intervals were presented for the respective ciclesonide/placebo ratios in addition to hypothesis testing. Treatment differences on the 7 days were tested by means of a closed testing procedure without need to adjust the α-level:[11] first day 7 and, if there was a significant difference between ciclesonide and placebo, day 6, and so on backward to day 1.

Secondary variables were the subjective nasal findings of obstruction, itching, and rhinorrhea. Obstruction was analyzed in analogy to the rhinal flow as both parameters provide information about the symptom obstruction—rhinal airflow as an objective parameter and the obstruction score as a subjective parameter. For the itching and rhinorrhea scores ascertained on study day 7, 95% confidence limits were calculated for the difference ciclesonide-placebo using an additive model. This evaluation was performed separately for the time points 5 minutes and 30 minutes after allergen provocation since the itching and rhinorrhea scores were generally lower at 30 minutes as compared to 5 minutes (in contrast to rhinal airflow and the obstruction score for which similar values were obtained). No adjustment of the α-level was made for the testing of these multiple secondary variables due to their exploratory nature.

Results of safety measurements at pre- and final check were analyzed in a merely descriptive manner. Clinical laboratory data were presented on an individual basis and were marked according to the normal ranges. Nature, incidence, intensity, and causality assessment were reported for each adverse event.

In this crossover study, the intrasubject coefficient of variation for the primary variable rhinal flow was approximately 35%. The chosen sample size of $N = 24$ subjects was sufficient to ensure a power of 80% in correctly declaring a change of 20% versus placebo as being significant at the 5% level, two-sided.

Organization of the Study

The study was conducted according to the revised Declaration of Helsinki, in compliance with the German Medicines Act and the requirements of good clinical practice (GCP).[12] The subjects were given comprehensive verbal and written information about objectives and possible risks of the study. They gave a written informed consent before the start and had the right to withdraw from the study at any time, even without giving the reasons. The study protocol was approved by the independent Ethics Committee of the Faculty of Clinical Medicine Mannheim of the University of Heidelberg. The clinical part of the study was conducted at the Mannheim University Hospital, Germany. The study was sponsored by Byk Gulden Pharmaceuticals, Konstanz, Germany.

RESULTS

All subjects completed the study according to protocol, and no subjects were replaced. The median percentage decrease in rhinal airflow after allergen provocation at screening was 40% (range: 26%-84%).

Efficacy Analysis

The time courses of geometric mean rhinal flow values (averages of 5 and 30 minutes) and SEM are plotted in Figure 2. On study days –2 and –1 (run-in phase with allergen challenge), the rhinal airflow was equivalent between ciclesonide (geometric mean: 508 and 520

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