

Construction of an Environmental Exposure Unit and Investigation of the Effects of Cetirizine Hydrochloride on Symptoms of Cedar Pollinosis in Japan

T Enomoto,¹ T Ide,² S Ogino³

¹Department of Otolaryngology, Red Cross Society, Wakayama Medical Center, Wakayama-City, Japan

²Department of Chemistry, Nara Medical University, Kashihara-City, Nara, Japan

³Graduate School of Allied Health Sciences, Osaka University Faculty of Medicine, Osaka, Japan

■ Abstract

Background: Cedar pollinosis is a widespread seasonal allergy that is unique to Japan. Environmental exposure units (EEU) assist in the development of effective therapeutic and preventive measures because outdoor studies are limited by seasonal variation in pollen exposure.

Objectives: We constructed an EEU to conduct a randomized cross-over double-blind placebo-controlled study of the efficacy of cetirizine (Zyrtec), a second-generation antihistamine.

Methods: The spatial and temporal homogeneity of pollen distribution in the EEU was evaluated by counting the number of pollen grains on petroleum-jelly-smear glass slides and by real-time pollen monitors. In the clinical study, 20 volunteers with known cedar pollinosis were exposed to pollen for 5 hours, randomly allocated to receive either cetirizine hydrochloride or placebo 30 minutes after exposure. Symptoms and the degree of somnolence were recorded every 30 minutes for 5.5 hours. As a measure of psychomotor performance, the Uchida-Kraepelin test was used to determine work quantity and error rate.

Results: The cedar pollen grains were scattered evenly in the exposure room. In the clinical study, symptom scores were elevated in both groups, showing significant symptom induction 30 minutes after exposure. Test drugs were administered 30 minutes after exposure, and 1 hour later patients in the cetirizine hydrochloride group experienced a significant decrease in sneezing, nose-blowing frequency, and nasal congestion compared with the placebo group. There were no significant differences between the 2 groups in terms of subjective somnolence or objective psychomotor performance.

Conclusion: The first EEU in Japan was used successfully to evaluate cetirizine as a treatment for cedar pollinosis. The results confirmed those from studies in other countries, except for the degree of somnolence, which increased in both groups and may have been related to postprandial sleepiness.

Key words: Japanese cedar pollinosis. Cetirizine. Environmental exposure unit. Second-generation antihistamine.

■ Resumen

Antecedentes: La polinosis por cedro es una alergia estacional muy extendida y exclusiva del Japón. Las unidades de exposición medioambiental ayudan a desarrollar medidas preventivas y terapéuticas eficaces, porque los estudios al aire libre se encuentran limitados por la variación estacional en la exposición al polen.

Objetivos: Creamos una unidad de exposición medioambiental para llevar a cabo un estudio aleatorio controlado con placebo y de doble ciego, con grupos cruzados, para comprobar la eficacia de la cetirizina (Zyrtec), un antihistamínico de segunda generación.

Métodos: Se evaluó la homogeneidad espacial y temporal de la distribución de polen en la unidad, contando la cantidad de granos de polen en un portaobjetos de vidrio cubierto de vaselina mediante monitorización del polen en tiempo real. Veinte voluntarios con polinosis por cedro se expusieron al polen durante cinco horas en el estudio clínico, a los que se asignó aleatoriamente a tratamiento con hidrocloreto de cetirizina o al grupo placebo a los 30 minutos de la exposición. Se registraron los síntomas y el grado de somnolencia cada 30 minutos durante cinco horas y media. Como medida del rendimiento psicomotor, se utilizó la prueba Uchida-Kraepelin para determinar la cantidad de trabajo y la tasa de error.

Resultados: Los granos de polen de cedro se repartieron de forma homogénea en la habitación de exposición. En el estudio clínico, las tasas de síntomas fueron elevadas en ambos grupos, siendo las manifestaciones significativas a los 30 minutos de la exposición. Los medicamentos de la prueba se administraron 30 minutos después de la exposición. Una hora después de la administración, los pacientes del grupo de hidrocloruro de cetirizina experimentaron un descenso significativo en los estornudos, en la frecuencia con que se sonaban la nariz y en la congestión nasal comparado con los voluntarios del grupo placebo. No se detectaron diferencias significativas entre los dos grupos en cuanto a somnolencia subjetiva o al rendimiento psicomotor objetivo.

Conclusión: La primera unidad de exposición medioambiental de Japón fue efectiva en la evaluación del tratamiento con cetirizina de la polinosis por cedro. Los resultados confirmaron los obtenidos en otros países, excepto en el grado de somnolencia, que aumentó en ambos grupos y que podría atribuirse a somnolencia posprandial.

Palabras clave: Polinosis por cedro japonés. Cetirizina. Unidad de exposición medioambiental. Antihistaminico de segunda generación.

Introduction

Allergy to Japanese cedar pollen is a common seasonal problem nationwide, affecting 16.2% of the population [1], and there is a high demand for effective preventive and therapeutic measures. The first preventive measure for allergy is, of course, to avoid the causative agent, but that is extremely difficult and so drugs are widely used. Outdoor trials have been conducted in Japan and other countries to evaluate the efficacy of medications for the symptoms of hay fever [2-4], but such studies are limited in value because it is difficult to achieve a consistent and sustained level of exposure, they are affected by the weather, and can only be conducted during the relevant season. It is therefore advantageous to expose subjects to a constant pollen level in a controlled environment for more reliable evaluation of therapeutic interventions.

Allergen environmental exposure units (EEUs) have been constructed in Austria [5], Canada [6], the United States of America [7], and Germany [8]. Generally, they are of simple construction, with fans and ducts to disperse the pollen uniformly and seating so that subjects can spend a certain period of time inside the unit. The pollen concentration can be regulated within the range of 200 to 1000 grains/m³, and the level monitored regularly. A comprehensive review on allergen challenge chambers was published in 2006 [9].

We established the first EEU in Japan in Wakayama Prefecture in order to evaluate the efficacy of treatments for cedar pollinosis, which is unique to Japan. We used the unit to conduct a randomized placebo-controlled, double-blind, crossover trial of the antihistamine cetirizine (Zyrtec, UCB Japan, Tokyo, Japan). Cetirizine is the most widely used second-generation antihistamine in the world, and many studies have confirmed its utility in the treatment of seasonal allergic rhinitis. Overseas pollen exposure unit experiments have also confirmed the effectiveness of cetirizine, making it suitable for use in the first EEU study in the context of cedar pollinosis conducted in Japan.

Methods

Construction of the EEU

We constructed a unit that can accommodate up to 30 subjects in a warehouse-style building larger than the Vienna challenge

chamber in Austria [5], which accommodates 14 people, but smaller than the Canadian unit [6], which can take up to 160. Other units can be found in Atlanta [7], and Copenhagen [10].

The Wakayama EEU has an open-style, hexagonal exposure room, with a floor area of 30 m², walls 2.1 m high, and a hexagonal conical roof that is 6 m at its highest point. All internal surfaces are wet washable. There is an anteroom, with an air shower between it and the entrance to the exposure room to remove pollen from people leaving the exposure room (Figure 1), and both rooms are kept at a slightly negative pressure to prevent pollen from escaping as subjects enter and leave via an air lock. Air supplied to the exposure room passes through a high-efficiency particulate air filter (VH-100-135P, Japan Vilene Co, Ltd, Tokyo, Japan). This type of air filter can theoretically remove at least 99.99% of dust, pollen, mold, bacteria and any airborne particles with a size of 0.3 μm. The temperature (20°–26° C) and humidity (50%–65%) are regulated by 2 air conditioners independent of the pollen dispersal system. Up to 30 sets of desks and chairs can be placed in the exposure room and subjects may read, work, watch the video monitor or listen to radio through earphones.

Cedar Pollen Dispersal

Japanese cedar pollen grains have a diameter of 20 to 30 μm and are relatively heavy; therefore, to maintain an even concentration of pollen within the exposure room without the need for vigorous air mixing, we decided to use a vertical flow system that feeds pollen into the room from the ceiling, to provide the exposure room with air that has a set pollen concentration supplied at a constant flow rate. In this system dehumidified and dust-filtered air is sent from an air compressor to the pollen feeder at a flow rate of 30 L/min by a flow controller. The pollen feeder, which is a dust feeder (Shibata Scientific Technology Ltd, Tokyo, Japan) that has been modified for use with pollen, transports the pollen to the dispersal unit in the middle of the ceiling of the exposure room where it is agitated in a spiral fashion. Finally, air conditioners disperse the pollen throughout the room.

Measurement of Pollen Concentrations

We used 2 methods to determine if pollen was evenly distributed throughout the room. Pollen concentrations in

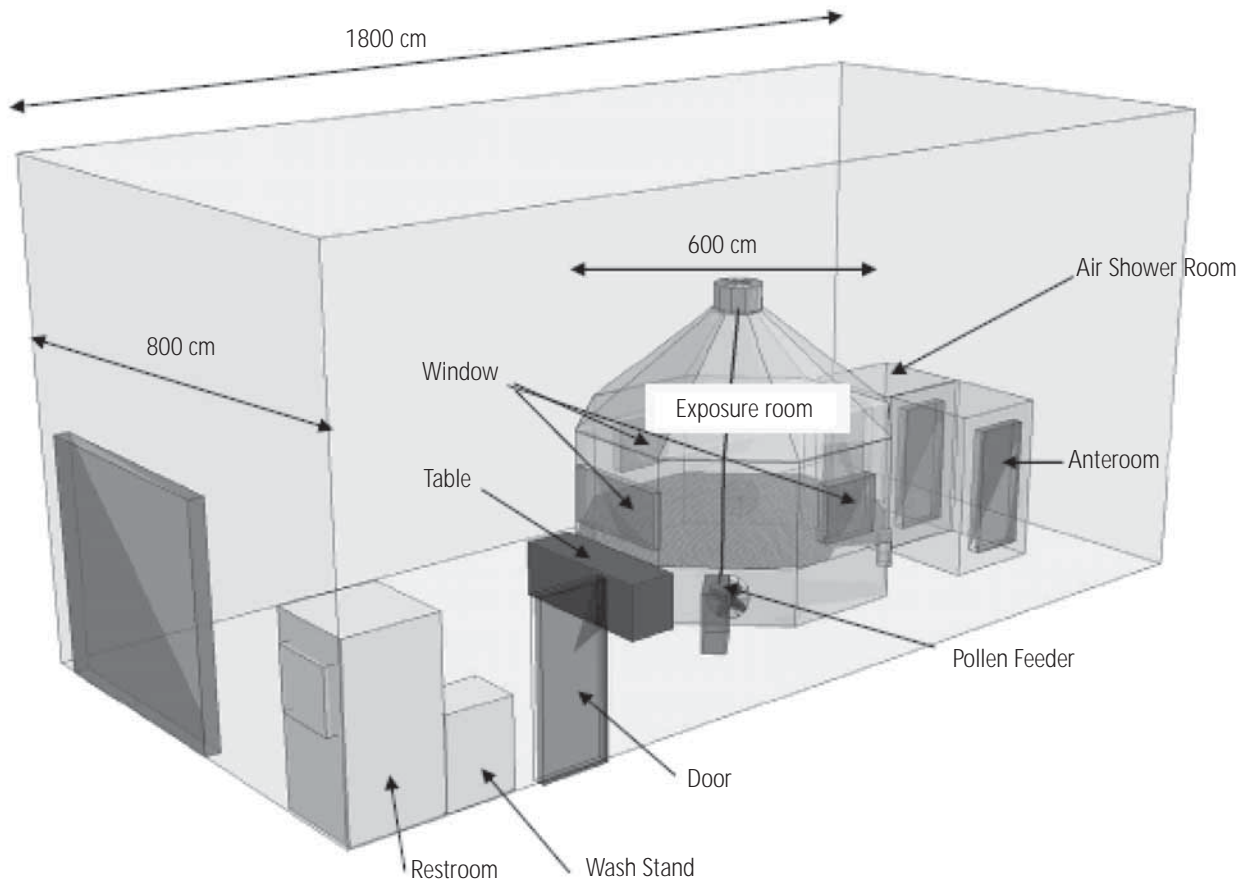


Figure 1. Design of the environmental exposure unit in Wakayama, Japan.

the exposure room were measured for a 40-minute period by real-time pollen monitors (particle monitor PC-300, Yamato Seisakusho Co, Ltd, Kanagawa, Japan) in 2 locations. The PC300 can detect horizontally dispersed particles 28 to 35 μm in size. Additionally, the number of pollen grains falling on petroleum-jelly-smeared glass slides was counted. The slides were placed in 17 locations (Figure 2) and the exposure room was maintained at 20°C and 65% humidity.

Clinical Study

Subjects: Twenty volunteers aged at least 20 years (10 men, 10 women; range, 20–50 years) previously diagnosed with cedar pollinosis and positive for specific immunoglobulin (Ig) E antibodies were enrolled after giving written informed consent. Excluded were subjects with asthma, with serious medical conditions such as hepatic, renal, or cardiac disorders, who were pregnant or might be pregnant or breastfeeding, and any other subjects considered unsuitable for the study by a physician.

The study was approved by the ethics committee of the nonprofit organization Japan Health Promotion Supporting Network.

Study groups: The test drugs were cetirizine hydrochloride

10 mg and placebo (vitamin B² formulation). Subjects underwent a 1-week washout period during which they ceased using antihistamine medications, medications with an antihistaminic effect or any other medications for allergic rhinitis that might influence the study results. The washout period of 7 days was based on unpublished preliminary data that showed the delayed response disappears completely within 2 to 3 days, and the plasma elimination half-life of cetirizine is 6.7 hours.

Although subjects are sometimes asked to wear clean-room suits, we did not ask our subjects to do so because particles released when they entered or left the exposure room had no effect on the real-time pollen counts, and we believed the subjects would be likely to be less anxious about the study if allowed to wear their own clothes.

The time course of clinical study is shown in Figure 2. On the day of the exposure trial the subjects entered the exposure room at 9:00 AM and underwent the Uchida–Kraepelin test [11,12] as a measure of psychomotor performance. Exposure to cedar pollen commenced 30 minutes later and continued for a 5-hour period from 9:30 AM to 2:30 PM. The test drugs were administered 30 minutes after commencement of pollen exposure, at 10:00 AM, and symptoms and the degree of somnolence were recorded immediately and then at 30-minute intervals for 5.5 hours from

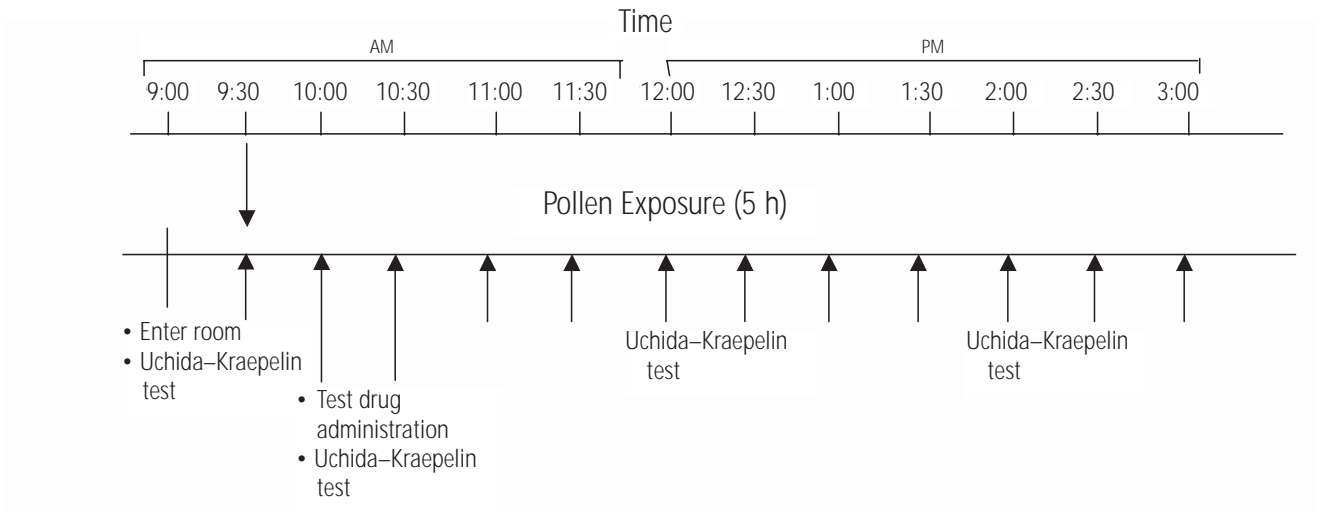
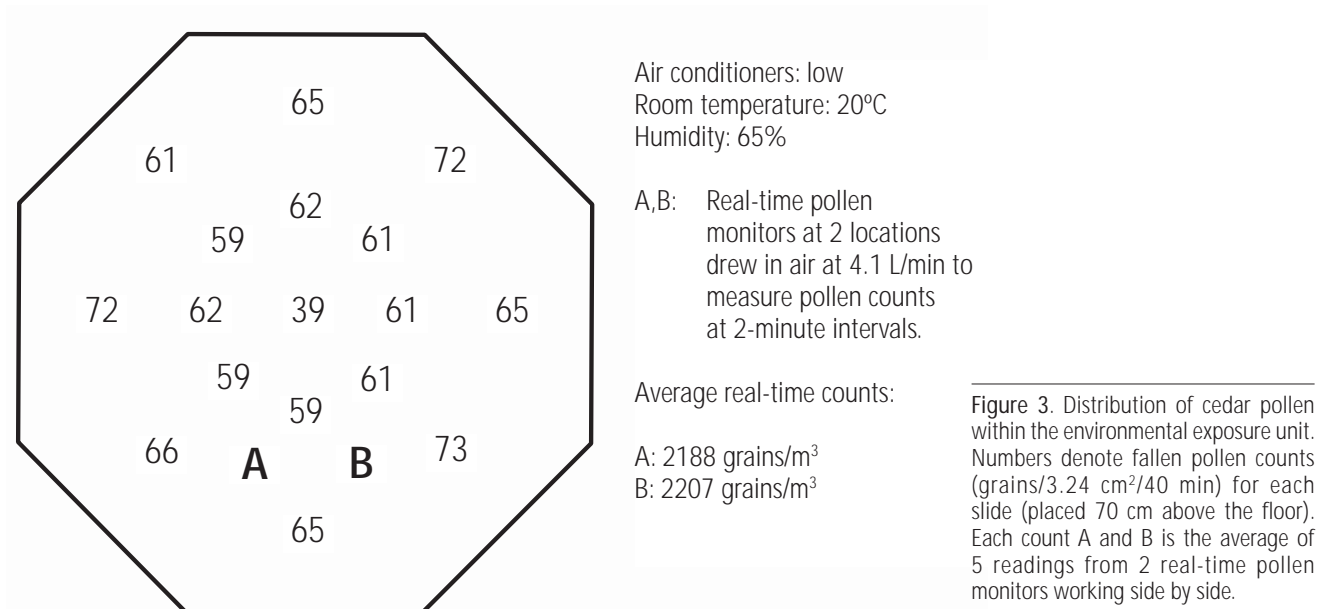


Figure 2. Protocol of the clinical study.



9:30 AM to 3:00 PM. The subjects took the Uchida–Kraepelin test immediately after test drug administration, 2 hours later, and again 4 hours later (10:00 AM and 12:00 AM and 2:00 PM). Subjects sat at the same desk throughout the study. Two weeks after the first study, subjects attended the Wakayama EEU for another study in which they were administered the other drug (crossover study) after the aforementioned 1-week washout.

Outcome measures: The test parameters were clinical symptoms, psychomotor performance, and somnolence.

Every 30 minutes the subjects recorded the number of times they had sneezed and blown their nose, and recorded the degree of “stuffy nose,” “itchy nose,” and ocular symptoms (including tears and itchiness) on a 10-cm visual analogue scale (VAS: 0 = no symptoms to 10 = unbearable), based on that used by Hyo et al [13].

Although the Uchida–Kraepelin test involves continuous addition of single-digit numbers, changing lines every minute, for 15 minutes, a short rest period, and a further 15 minutes of addition, only a single period of addition was conducted in this study. The number of calculations and mistakes were counted.

The degree of somnolence was recorded on a 10-cm VAS (0 = not sleepy to 10 = unbearably sleepy) [13].

Statistical Analyses

Scores for each group at each time point for symptoms and psychomotor function were recorded as mean ± SD. Results were analyzed using Wilcoxon rank-sum test, and a probability value less than 5% was considered to indicate a significant difference.

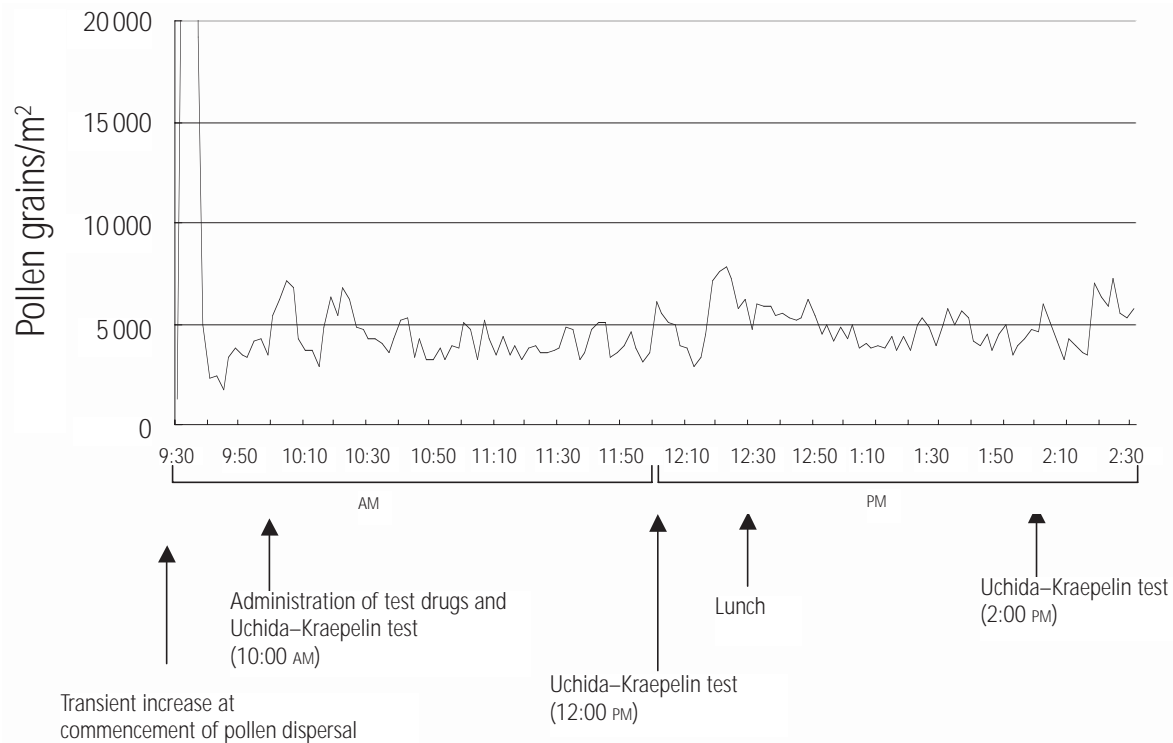


Figure 4. Changes in cedar pollen levels during the 5-hour clinical study.

Results

Distribution of Cedar Pollen in the EEU

Figure 3 (pollen counts with no people present in the room) shows that although the count on the center-placed slide was lowest at 39 grains/3.24 cm², counts on the remaining glass slides ranged from 59 to 73 grains/3.24 cm², an extremely small dispersion compared with the total amount of airborne pollen. The 2 real-time pollen monitors working side by side under the same conditions confirmed an even distribution of airborne pollen, with average counts of 2188 grains/m³ and 2207 grains/m³, respectively. Thus the slide measurements confirmed even spatial pollen distribution, and the real-time monitors confirmed even temporal distribution. Figure 4 shows the results of monitoring airborne pollen levels over the 5-hour period of pollen exposure using the average readings from monitor A (Figure 3) on the 2 study days. Apart from a transient sharp increase in pollen immediately following activation of the dispersal system, reflecting initial release of pollen contained within the system and minor temporary disturbances as people enter and leave the room, the pollen level remained constant.

Clinical Symptoms

This study was conducted on August 7 and 20, 2005, and the level of airborne cedar pollen within the exposure room

was set at approximately twice the peak level experienced in Wakayama City in the spring of 2005.

The time course of clinical symptoms induced by cedar pollen exposure is shown in Figure 5. By 30 minutes after exposure (10:00 AM), there was significant symptom induction in the form of greater frequency of sneezing, nose-blowing, nasal congestion, and nasal itchiness in both the cetirizine and placebo groups compared with immediately post-exposure (9:30 AM). In the cetirizine group, 30 minutes after drug administration, there was a significant reduction in the frequency of sneezing compared with pre-administration, and 1 hour after administration the frequency of both sneezing and nose-blowing was significantly reduced compared with the placebo group. This effect was maintained until the subjects left the exposure room. The most marked difference between groups was in the nasal congestion symptom score, which rose steadily in the placebo group following exposure, whereas in the cetirizine group it was significantly lower 30 minutes after drug administration than in the placebo group; 90 minutes after administration it was significantly lower in the treatment group than in the placebo group and also lower than the pre-administration score. Similarly, the nasal itchiness symptom score rose in the placebo group following exposure, whereas in the cetirizine group it decreased steadily after administration. Initially, there was little difference between the groups in ocular symptoms, but by the time subjects left the exposure room (3:00 PM) a significantly lower symptom score was seen in the cetirizine group compared with the placebo group.

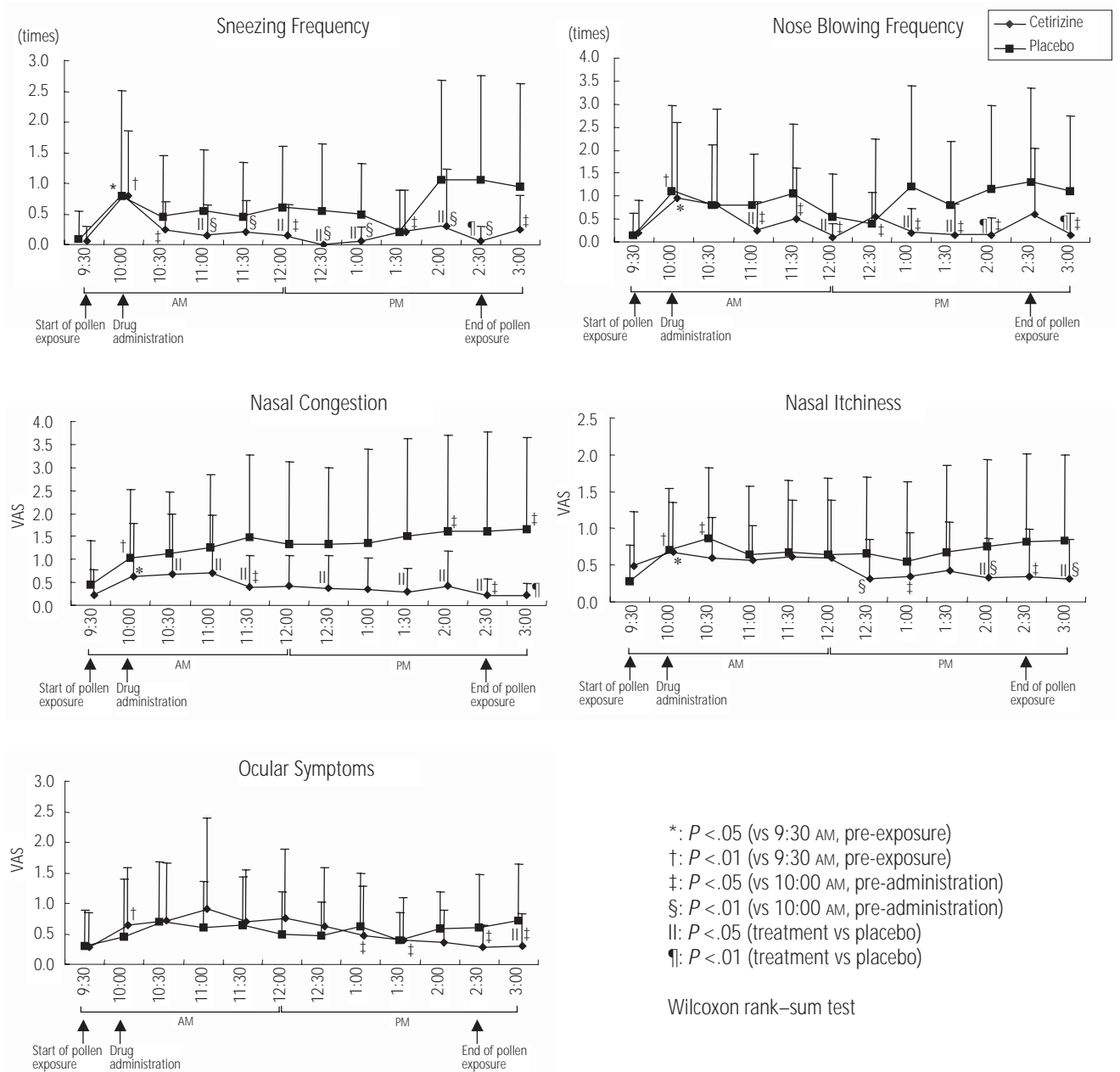


Figure 5. Time course of the clinical symptoms. VAS indicates visual analog scale.

Assessment of Somnolence and Psychomotor Performance

The time course of subjective somnolence was similar for both groups, gradually increasing following exposure (Figure 6). The results of Uchida–Kraepelin testing showed that in both groups work quantity increased gradually and the number of mistakes and error rate tended to decrease (Figure 7). All tested parameters were slightly higher in the cetirizine group, although the difference was not significant.

Discussion

The incidence of all allergic conditions, including hay fever, is increasing in Japan and cedar pollinosis in particular now affects more than 16.2% of the population, making it a “national disease,” and there has been a corresponding massive increase in the demand for effective treatments. At present, the only treatment that can be said to even temporarily “cure” allergy symptoms is immunotherapy, which is limited by the long course of treatment required before the onset of effect, and the risk of generalized reactions such as anaphylactic shock. For

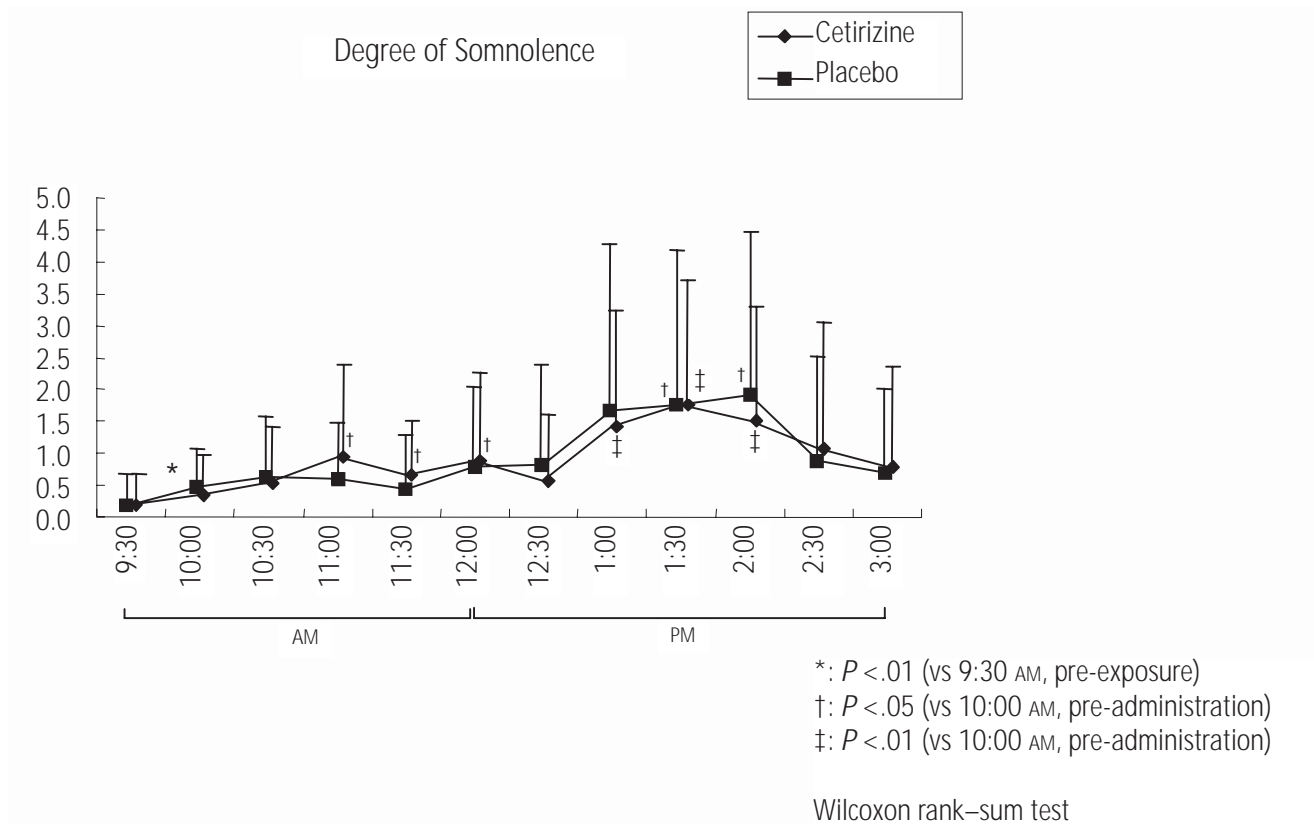


Figure 6. Subjective assessment of somnolence.

these reasons, medication is the mainstay of treatment and new drugs that are highly efficacious, but comparatively nonsedating, have been developed worldwide. The efficacy of medications in the treatment of hay fever has largely been evaluated in outdoor trials [2-4], but because the level of airborne pollen varies from year to year and is also affected by the weather on the day of the study and the locale, EEU's have been developed around the world [5-10] in order to reproduce natural induction of allergic reactions in a controlled indoor setting.

With the assistance of the Japan Health Promotion Supporting Network, we established the first fully functional EEU in Japan. We decided to accommodate 30 people because we considered that a larger room may have greater variation in the pollen count, as reported by the Canadian experience in which the variability was 3500 ± 500 grains/m³ [6]. Furthermore, because Japanese cedar pollen grains are particularly heavy, making it difficult to achieve even dispersal with a wall-mounted pollen feeder, we chose a vertical-flow ceiling feed system to ensure constant, even pollen distribution within the exposure room. Although the results of monitoring airborne pollen levels over the 5 hours showed a transient sharp increase at the time of starting dispersion (for 5-6 minutes), this was merely a characteristic of this feeder system, and we consider that it did not have an effect on the 5-hour study overall.

Although the clinical study was conducted in August 2005, which is not the usual hay fever season, typical symptoms were successfully induced with an airborne level of cedar pollen

approximately twice the peak levels experienced in Wakayama City in the spring of 2005. Out of consideration for the subjects' well-being, exposure was limited to 5 hours. There was a significant decrease in symptoms in the subjects given cetirizine. Similarly, Day et al [14] conducted a study on 2 days and reported a significant reduction in symptom scores for cetirizine versus placebo 1 hour after drug administration and we can confirm a typically rapid onset of action for cetirizine in the present study.

We used a subjective assessment of somnolence and the scores for both groups rose gradually, with no significant difference. This result is consistent with the comparatively nonsedating properties of cetirizine hydrochloride, although the reason for the gradual increase in somnolence in both groups is unclear. It may be related to postprandial somnolence as the increase occurred in the afternoon.

In the present study we used the Uchida-Kraepelin testing [11] as a measure of psychomotor function. Although this test was developed for psychodiagnostic purposes in Japan, it has been used in the phase I study of an anti-anxiety drug in order to evaluate psychomotor function [12]. Oguchi et al [15] reported that in their study of chlorpheniramine, a proprietary cold remedy, they used Uchida-Kraepelin testing as an objective measure of sleepiness and found a significant reduction in work quantity 2 hours after administration compared with before administration. Based on those results, we measured work quantity, number of mistakes and error rates, anticipating that the induction of hay fever

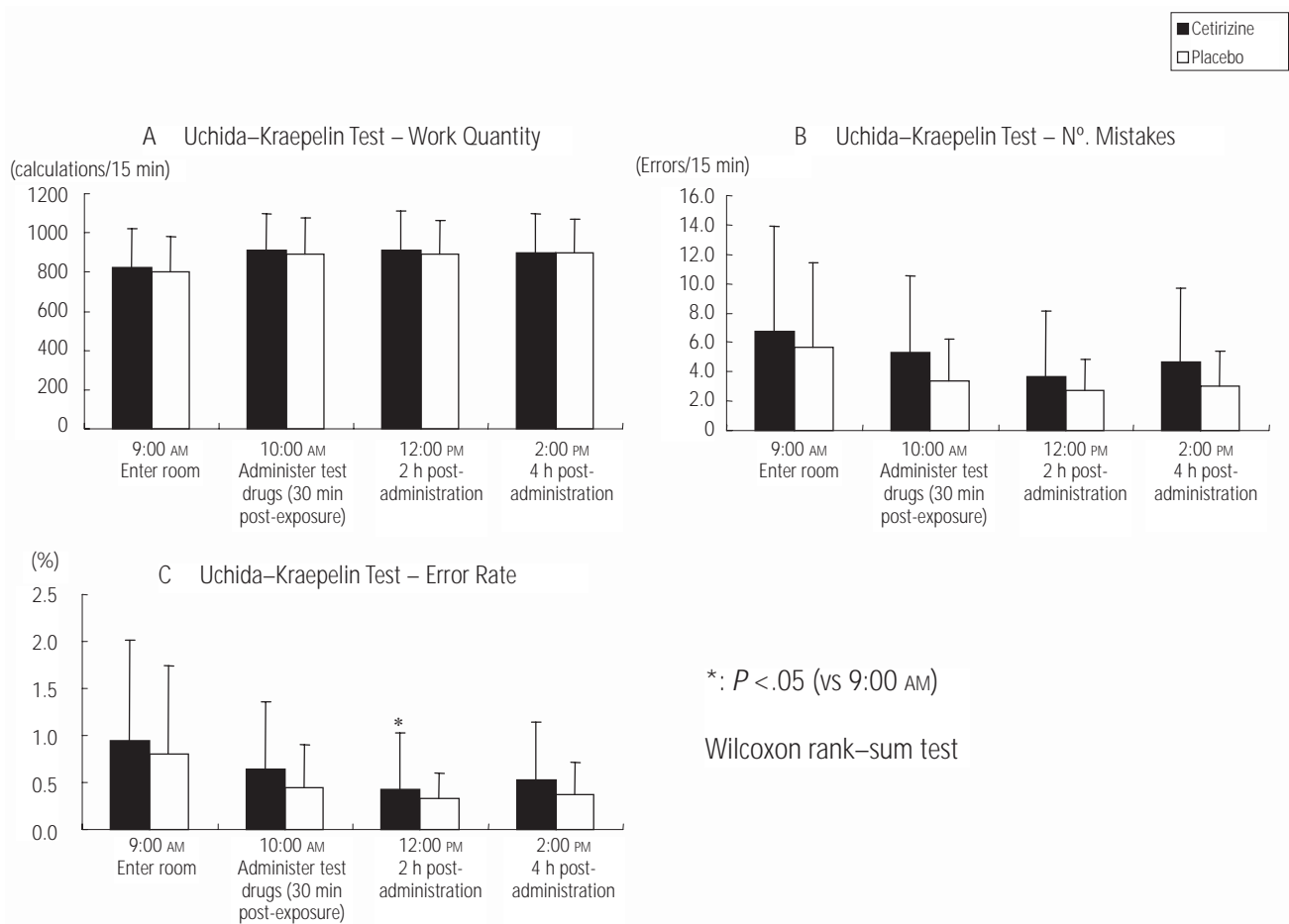


Figure 7. Psychomotor functional assessment of work output and accuracy.

symptoms would make calculations more difficult and hence work quantity in the placebo group would decrease with a corresponding increase in the number of mistakes and error rate. The actual results were not as anticipated, perhaps because more severe symptoms are required before work is affected. Further study is needed in this area, although our findings that cetirizine did not reduce work quantity, and that there was no significant difference between the cetirizine and placebo groups, indicate that cetirizine has little effect on the central nervous system.

The first EEU in Japan was used successfully to evaluate the efficacy of cetirizine, a second-generation antihistamine, for cedar pollinosis. We will continue to use the unit to assess the efficacy of therapeutic and preventive interventions for hay fever. With further elucidation of the mechanism of cedar pollinosis, we hope to assist the many sufferers who are looking for safe, effective treatments.

References

- Baba K, Konno A, Takenaka H. [Allergic Rhinitis Therapeutic Guidelines Preparation Committee: Allergic rhinitis therapeutic

guidelines: perennial rhinitis and hay-fever, 2005 edition, 5th revision (in Japanese)] Tokyo: Life Science; 2005.

- Meltzer EO, Weiler JM, Widlitz MD. Comparative outdoor study of the efficacy, onset and duration of action, and safety of cetirizine, loratadine, and placebo for seasonal allergic rhinitis. *J Allergy Clin Immunol.* 1996;97:617-26.
- Hyo S, Fujieda S, Kawada R, Kitazawa S, Takenaka H. The efficacy of short-term administration of 3 antihistamines vs placebo under natural exposure to Japanese cedar pollen. *Ann Allergy Asthma Immunol.* 2005;94:457-64.
- Asaga H, Yoshida H, Baba K. [Clinical efficacy of Ebastin in the treatment of cedar pollinosis in an outdoor comparative study (in Japanese)] *Arerugi.* 2002;51:357-63.
- Horak F, Stubner P, Zieglmayer R, Kavina A, De Vos C, Burtin B, Donnelly F. Controlled comparison of the efficacy and safety of cetirizine 10 mg o.d. and fexofenadine 120 mg o.d. in reducing symptoms of seasonal allergic rhinitis. *Int Arch Allergy Immunol.* 2001;125:73-9.
- Day JH, Briscoe MP, Clark RH, Ellis AK, Gervais P. Onset of action and efficacy of terfenadine, astemizole, cetirizine, and loratadine for the relief of symptoms of allergic rhinitis. *Ann Allergy Asthma Immunol.* 1997;79:163-72.
- Berkowitz RB, Woodworth GG, Lutz C, Weiler K, Weiler J,

- Moss M, Meeves S. Onset of action, efficacy, and safety of fexofenadine 60 mg/pseudoephedrine 120 mg versus placebo in the Atlanta allergen exposure unit. *Ann Allergy Asthma Immunol.* 2002;89:38-45.
- 8 Krug N, Loedding H, Hohlfeld JM, Larbig M, Buckendahl A, Badorrek P, Geldmacher H, Behnke W, Dunkhorst W, Windt H, Luettig B, Koch W. Validation of an environmental exposure unit for controlled human inhalation studies with grass pollen in patients with seasonal allergic rhinitis. *Clin Exp Allergy.* 2003;33:1667-74.
- 9 Day JH, Horak F, Briscoe MP, Canonica GW, Fineman SM, Krug N, Leynadier F, Lieberman P, Quirce S, Tanenaka H, Van Cauwenberge P. The role of allergen challenge chambers in the evaluation of anti-allergic medication: an international consensus paper. *Clinical & Experimental Allergy Reviews.* 2006;6:31-59.
- 10 Ronborg SM, Mosbech H, Johnsen CR, Poulsen LK. Exposure chamber for allergen challenge. The development and validation of a new concept. *Allergy.* 1996;51:82-8.
- 11 Kuraishi S, Kato M, Tsujioka B. Development of the "Uchida-Kraepelin psychodiagnostic test" in Japan. *Psychologia.* 1957;1:104-9.
- 12 Murasaki M, Miura S, Ishigooka J, Ishii Y, Takahashi A, Fukuyama Y. Phase I study of a new antianxiety drug, buspirone. *Prog Neuropsychopharmacol Biol Psychiatry.* 1989;13:137-44.
- 13 Hyo S, Fujieda S, Kawada R, Kitazawa S, Takenaka H. The efficacy of short-term administration of 3 antihistamines vs placebo under natural exposure to Japanese cedar pollen. *Annals of allergy, asthma, and immunology.* 2005;94:457-65
- 14 Day JH, Briscoe M, Widlitz MD. Cetirizine, loratadine, or placebo in subjects with seasonal allergic rhinitis: effects after controlled ragweed pollen challenge in an environmental exposure unit. *J Allergy Clin Immunol.* 1998;101:638-45.
- 15 Oguchi K, Uchida E, Kobayashi S, Yasuhara H. Clinical pharmacological study of Veganin, a proprietary cold remedy: Evaluation of sleepiness with psychomotor performance tests. *J Clin Ther Med.* 1988;4:839-49.
- *Manuscript received September 25, 2006; accepted for publication November 23, 2006.*
- **Tadao Enomoto, MD**
- Department of Otolaryngology, Red Cross Society
Wakayama Medical Center
4-20 Komatsubara
Wakayama-City, Japan
E-mail: t-enomoto@mud.biglobe.ne.jp