Allergology International. 2008;57:257-263
DOI: 10.2332/allergolint.O-07-525

ORIGINAL ARTICLE

Evaluation of Efficacy and Sedative Profiles of H_1 Antihistamines by Large-Scale Surveillance Using the Visual Analogue Scale (VAS)

Norimasa Izumi[1], Hiroyuki Mizuguchi[1], Hayato Umehara[1], Satoshi Ogino[2] and Hiroyuki Fukui[1]

ABSTRACT

Background: H_1 antihistamines are widely used as therapeutics for allergic diseases. Sedation is a well-known side effect of H_1 antihistamines and sometimes it is life-threatening for patients. Thus it is important to evaluate the sedative properties of H_1 antihistamines to avoid side effects. For this purpose, histamine H_1 receptor (H1R) occupancy and proportional impairment ratios (PIR) are now being used. However, it is not easy to obtain these parameters. Here, we sought to evaluate the sedative properties of H_1 antihistamines by means of a large-scale surveillance at health insurance pharmacies.

Methods: The survey was conducted at 37 health insurance pharmacies. The therapeutic efficacy and the degree of sleepiness were quantified through a questionnaire using the visual analog scale (VAS) directly from 1742 patients who received H_1 antihistamines.

Results: The degree of sleepiness caused by the first-generation antihistamines was significantly higher than that of the second-generation antihistamines. The high VAS score in case of efficacy was found in *d*-chlorpheniramine, olopatadine, and ebastine. Among the mean values of efficacy, all second-generation antihistamines except for loratadine, bepotastine, and mequitazine were significantly higher than that of clemastine. Regarding the degree of sleepiness, clemastine scored the highest VAS score, and significantly lower scores were obtained in all second-generation antihistamines.

Conclusions: The sedative properties of the H_1 antihistamines obtained from VAS analysis were very similar to those of H1R occupancy from positron emission tomography (PET) studies and PIR from meta-analysis. Our results indicate that large-scale surveillance using VAS might be useful to evaluate the profiles of H_1 antihistamines.

KEY WORDS

antihistamines, efficacy, questionnaire, sleepiness, visual analogue scale

ABBREVIATIONS

H1R, histamine H_1 receptor; VAS, visual analogue scale; PET, positron emission tomography; PIR, proportional impairment ratios

INTRODUCTION

Histamine is a major chemical mediator in the pathogenesis of allergic diseases. Activation of the histamine H_1 receptor (H1R) by histamine causes many symptoms of allergic diseases including sneezing, watery rhinorrhea, and itching, which can be effectively blocked by H_1 antihistamines that antagonize the action of histamine. Thus H_1 antihistamines are widely used as the primary therapeutics for allergic dis-

[1]Department of Molecular Pharmacology, Institute of Health Biosciences, The University of Tokushima Graduate School, Tokushima and [2]Graduate School of Allied Health Sciences, Faculty of Medicine, Osaka University, Osaka, Japan.
Correspondence: Hiroyuki Fukui, Department of Molecular Pharmacology, Institute of Health Biosciences, The University of Tokushima Graduate School, 1–78–1 Shomachi, Tokushima 770–8505, Japan.
Email: hfukui@ph.tokushima–u.ac.jp
Received 7 November 2007. Accepted for publication 31 January 2008.

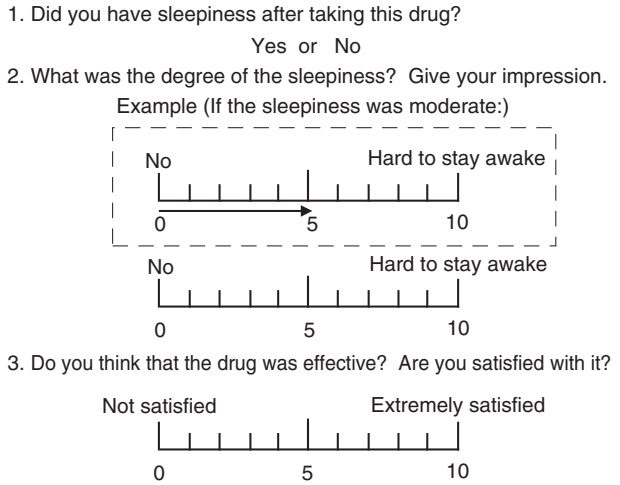

Fig. 1 Questionnaire and visual analog scale used in this study.

eases.

Sedation is one of the most frequent side effects in prescription medications (POM) and over-the-counter (OTC) medications for allergic diseases. It has been well documented that the sedation is caused by penetration of H_1 antihistamines into the blood-brain barrier and consequently blocking the function of the brain histaminergic system mediated by H1R.[1] H_1 antihistamines are classified into two categories, the first-generation antihistamines and the second-generation antihistamines. The first-generation antihistamines, such as *d*-chlorphemiramine and clemastine are considered to cause strong sleepiness as an adverse reaction due to readily crossing the blood-brain barrier, whereas the adverse reaction of the second-generation antihistamines, such as fexofenadine and epinastine is considered less severe because these drugs do not cross blood-brain barrier readily. This sedative side effect induces psychomotor retardation and causes potentially life-threatened problems for patients involved in driving or operating heavy machinery, even at recommended doses.[2] So it is important to evaluate the sedative properties of H_1 antihistamines. Yanai *et al*. have shown that there is a significant correlation between cognitive decline and brain H1R occupancy induced by H_1 antihistamines using positron emission tomography (PET) with [^{11}C]doxepin.[3-7] Shamsi and Hindemarch have demonstrated that proportional impairment ratios (PIR) obtained by meta-analysis of H_1 antihistamines are useful for comparison of their sedative properties, especially among the second-generation antihistamines.[8,9] Although these parameters are very useful to evaluate the properties of H_1 antihistamines, it is not easy to obtain them. PET apparatus are not available anywhere and it is not easy to collect enough data in a short time. Also calculation of PIR is not easy because all previous reports on sedation caused by H_1 antihistamines should be reviewed.[8]

Table 1 H_1 antihistamines used in this study

Generation	Drugs
First	*d*-Chrolpheniramine
	Clemastine
Second	Bepotastine
	Cetirizine
	Ebastine
	Epinastine
	Fexofenadine
	Loratadine
	Mequitazine
	Olopatadine

Here, we conducted a large-scale surveillance at health insurance pharmacies that dispense drug prescriptions for a wide retail chain, by obtaining information through a questionnaire using the Visual Analogue Scale (VAS) directly from patients who received H_1 antihistamines. The VAS is a method that can be readily understood by most people to measure a characteristic or attitude that cannot be directly measured. It was originally used in the field of psychometrics, and nowadays widely used to assess changes in patient health status with treatment.[10-13] In the present study, we quantified the therapeutic efficacy and the degree of sleepiness of H_1 antihistamines using VAS analysis. We also compared the sedative profiles obtained by our surveillance with those from PET studies and meta-analysis.

METHODS

In health insurance pharmacies (37 pharmacies) that dispense drug prescriptions, patients on therapy with a H_1 antihistamine for the treatment of nasal or skin diseases were requested at the time of medication instruction to complete a questionnaire (Fig. 1). The questionnaire was designed to compare the therapeutic efficacy and the degree of sleepiness occurring as an adverse reaction, using the VAS (maximum point: 10; minimum point: 0) as follows: Question 1, Did you have sleepiness after taking this drug? (yes or no); Question 2, What was the degree of the sleepiness? Give your impression (from 0 for no to 10 for hard to awake); Question 3, Do you think that the drug was effective? Are you satisfied with it? (from 0 for not satisfied to 10 for extremely satisfied). In cases where someone other than patients came to the pharmacy, the questionnaire was taken home and completed by the patient and collected at the next visit to the pharmacy. This study was conducted in the form of a direct interview of patients aged at least 9 years who themselves could provide information. Content of the questionnaire were as follows: age, occupation, name

Table 2 Characteristics of subjects

		The first-generation	The second-generation	All cases	Test
Number of cases		385	1357	1742	
Sex	Male	129	487	616	N.S.*
	Female	255	857	1112	
	Unknown	1	13	14	
Age	−9	0	9	9	$P < 0.001$
	10−19	30	146	176	
	20−29	48	219	267	
	30−39	42	226	268	
	40−49	40	215	255	
	50−59	79	164	243	
	60−69	77	184	261	
	70−	69	186	255	
	Unknown	0	8	8	

*not significant

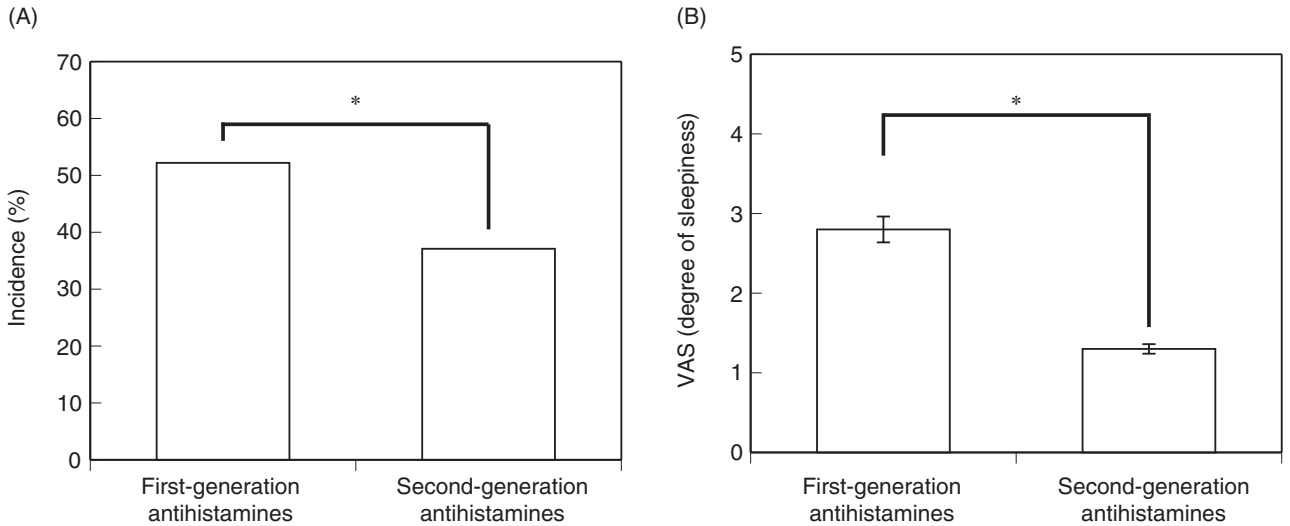

Fig. 2 Comparison of the incidence (**A**) and the degree (**B**) of sleepiness on the first- and second-generation antihistamines using VAS. The first-generation ($n = 385$) and the second-generation ($n = 1357$) antihistamines, respectively. χ^2 test for (**A**) , and unpaired t-test for (**B**) were used for statistical analysis. * $P < 0.001$.

of disease, presence or absence of sleepiness, degree of sleepiness, and therapeutic efficacy. The results are presented as mean ± standard error (SE). Data were analyzed using GraphPad Prism software (GraphPad Software, Inc., San Diego, CA). Unpaired t-test, χ^2 test or One-way ANOVA followed by Tukey's multiple comparison test was used for statistical analysis. P values less than 0.05 were considered significant.

RESULTS

DISPOSITION AND BACKGROUND OF PATIENTS

The questionnaire was collected from a total of 1865 patients (survey period: from June 2002 to September 2005). From these patients, those who used the H_1 antihistamines shown in Table 1 were selected, and those who used 2 or more H_1 antihistamines concomitantly were excluded. As a result, a total 1742 patients were analyzed, consisting of 385 patients who used the first-generation antihistamines and 1357 patients who used the second-generation antihistamines. The backgrounds of the 1742 patients are summarized in Table 2. A significant difference (by χ^2 test) between the first- and the second-generation antihistamines was found in age (Table 2) and occupation (not shown). Analysis of covariance using age or occupation as covariate was conducted because a sig-

Table 3 Summary of the efficacy and the degree of sleepiness of H_1 antihistamines

	Efficacy	Degree of sleepiness	Efficacy/Degree of sleepiness
First-generation antihistamines	6.20±0.13	2.82±0.16	2.2
d-Chrolpheniramine	7.04±0.25	2.06±0.26	3.4
Clemastine	5.80±0.16	3.07±0.21	1.9
Second-generation antihistamines	6.71±0.07	1.26±0.06	5.3
Bepotastine	6.36±0.24	1.03±0.18	6.2
Cetirizine	6.88±0.20	1.28±0.18	5.4
Ebastine	6.99±0.17	1.54±0.17	4.5
Epinastine	6.82±0.20	0.88±0.14	7.8
Fexofenadine	6.77±0.18	0.94±0.13	7.2
Loratadine	6.23±0.22	0.88±0.14	7.1
Mequitazine	6.34±0.23	1.54±0.25	4.1
Olopatadine	7.01±0.19	2.01±0.21	3.5

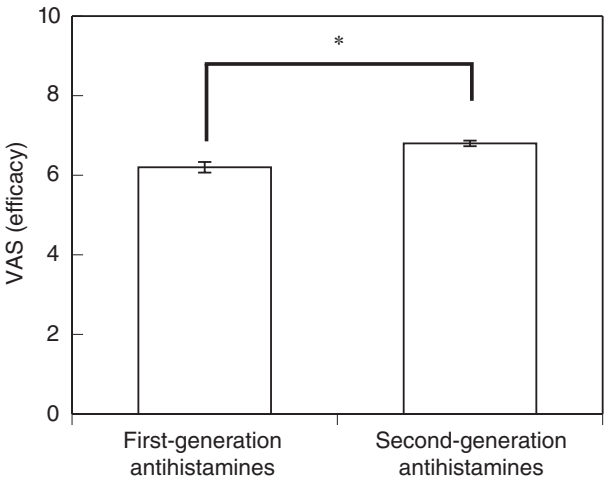

Fig. 3 Comparison of the efficacy on the first- and second-generation antihistamines using VAS. The first-generation (n = 385) and the second-generation (n = 1357) antihistamines, respectively. * $P < 0.001$ (unpaired t-test).

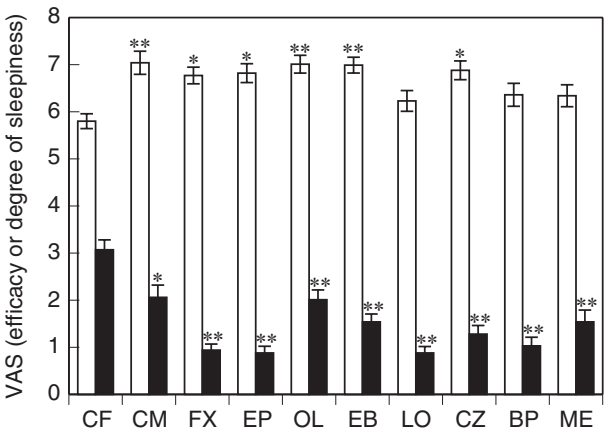

Fig. 4 Comparison of the efficacy and the degree of sleepiness of H_1 antihistamines. The VAS scales of the efficacy are shown as open columns and the VAS scales of the degree of sleepiness are shown as closed columns. One-way ANOVA followed by Tukey's multiple comparison test was used for statistical analysis. ** $p < 0.001$, and * $p < 0.01$ vs. clemastine. Abbreviations: CF, clemastine (n = 239); CM, *d*-chlorpheniramine (n = 117); FX, fexofenadine (n = 211); EP, epinastine (n = 168); OL, olopatadine (n = 163); EB, ebastine (n = 227); LO, loratadine (n = 168); CZ, cetirizine (n = 157); BP, bepotastine (n = 128); and ME, mequitazine (n = 79).

nificant difference was observed in age or occupation. Since no significant difference was found between the results before and after correction, we decided to present the data before correction as the results of this study.

COMPARISON BETWEEN THE FIRST- AND THE SECOND-GENERATION ANTIHISTAMINES

Both the incidence (Fig. 2A) and the degree (Fig. 2B) of sleepiness caused by the first-generation antihistamines were significantly higher than those of the second-generation antihistamines ($p < 0.001$). On the other hand, the mean values of efficacy of the second-generation antihistamines were significantly higher than that of the first-generation antihistamines (Fig. 3, $p < 0.001$). The ratio of efficacy/degree of sleepiness of the second-generation antihistamines was 2.4-fold higher than that of the first-generation antihistamines (5.3 vs. 2.2, Table 3).

COMPARISON BETWEEN DRUGS

As shown in Figure 4, the efficacies of *d*-chlorpheniramine, olopatadine, and ebastine were significantly higher than that of clemastine. Clemastine showed the lowest VAS score of 5.8. In the degree of sleepiness, clemastine showed the highest degree (VAS = 3.1) and all second-generation antihistamines showed

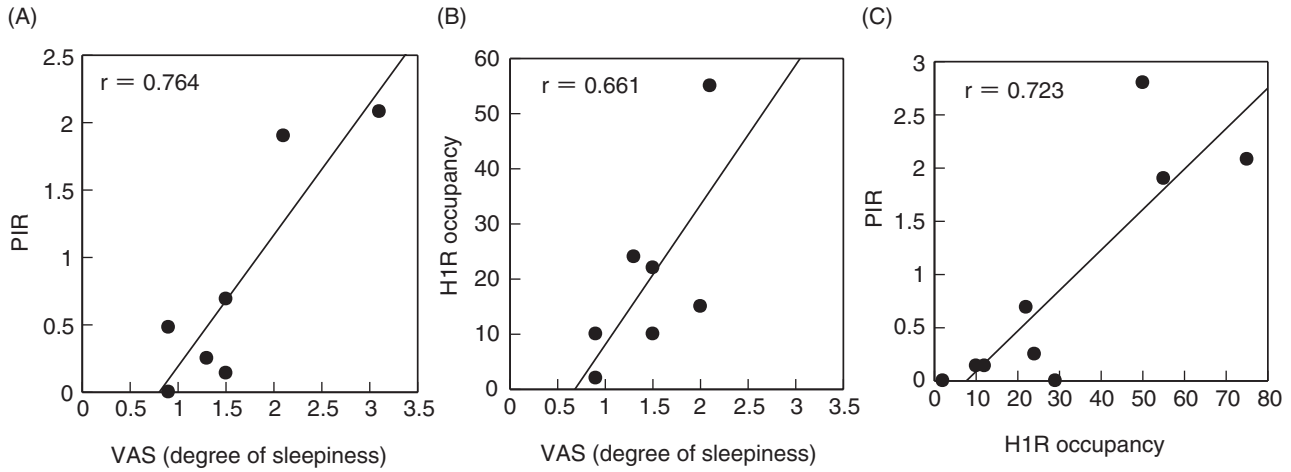

Fig. 5 Relationships among VAS scores for the degree of sleepiness caused by H_1 antihistamines, proportional impairment ratios (PIR), and H_1-receptor occupancies. The data of PIR were taken from ref. 8 and the data of H1RO were from ref. 7. Relationship between VAS scores and PIR (**A**), between VAS scores and H1R occupancies (**B**), and between H1R occupancies and PIR (**C**) are shown. Correlation was analyzed by Spearman's rank correlation test.

significantly lower degrees of sleepiness than that of clemastine. The VAS score of the second-generation antihistamine olopatadine (2.0) was a similar degree to that of the first-generation antihistamine *d*-chlorpheniramine (2.1). When we calculated the ratio of efficacy/degree of sleepiness for each H_1 antihistamines, epinastine showed a high ratio of 7.8, and fexofenadine and loratadine showed 7.2 and 7.1, respectively. Meanwhile, the ratios of the first-generation antihistamines, *d*-chlorpheniramine and clemastine were low (3.4 and 1.9, respectively). Among the second-generation antihistamines, olopatadine showed a relatively low efficacy/degree of sleepiness ratio (3.5).

RELATIONSHIPS BETWEEN VAS SCORES FOR THE DEGREE OF SLEEPINESS OF H_1 ANTIHISTAMINES AND PROPORTIONAL IMPAIRMENT RATIOS OR H_1-RECEPTOR OCCUPANCIES

The VAS sores of the degree of the sleepiness of H_1 antihistamines highly correlated with proportional impairment ratio (PIR; r = 0.764, Fig. 5A). Moderate correlation (r = 0.661, Fig. 5B) was found in the relationship between VAS scores of the degree of the sleepiness of H_1 antihistamines and H1R occupancy. As we expected, a strong correlation (r = 0.723, Fig. 5C) was observed in the relationship between PIR and H1R occupancy.

DISCUSSION

It is well known that histamine H_1 receptors modulate many physiological functions including wakefulness and the sleep-wake cycle.[14,15] Therefore, H_1 antihistamines inactivate the histaminergic neuron system and cause sedation that induces psychomotor retardation of patients. To maintain patient quality of life, H_1 antihistamines should be non-sedative. In the present study, we performed the large-scale surveillance (1742 patients) at 37 health insurance pharmacies that dispense drug prescriptions for a wide retail chain, and evaluated the efficacy and sedative profiles of H_1 antihistamines using VAS analysis. In the literature, there are some similar small-scale surveillance reports[13,16,17] (around 100), but there is no report with over 1,000 patients like this study. In small-scale surveillance, the results often contain unfavorable factors such as regional bias. In our surveillance, we performed VAS analysis at 37 stores locate throughout western Japan, so that we considered that such unexpected bias was negligible.

Our surveillance data showed that the VAS scores for incidence and degree of sleepiness of the first-generation antihistamines were significantly higher than those of the second-generation antihistamines ($p < 0.001$, Fig. 2). This result confirmed the generally accepted anti-sedative characteristic of second-generation antihistamines. The second-generation antihistamines also showed significantly ($p < 0.001$) higher VAS scores for the efficacy than those of the first-generation antihistamines (Fig. 3). These data indicate that the second-generation antihistamines predominate over the first-generation antihistamines. High efficacy found in the second-generation antihistamines might be due to their anti-allergic properties like inhibition of release of inflammatory mediators such as histamine, leukotrienes, and prostagrandines[18] in addition to the antihistamine effect. There was no correlation between the VAS scores of degree of sleepiness and efficacy (r = 0.194, data not shown). We calculated the ratio of efficacy/degree of sleepiness for each generation of antihistamine (Table 3). This ratio indicates how properly antihistamines

work, and antihistamines with higher ratios could be considered as better drugs for allergic diseases. The ratio of the second-generation antihistamines was 2.4-fold higher than that of the first-generation antihistamines indicating the predominance of the second-generation antihistamines.

Next, we examined the efficacy and the degree of sleepiness of the second-generation antihistamines by drugs. The mean value of sleepiness was low with fexofenadine, epinastine, and loratadine (VAS score = 0.9) indicating lesser adverse reaction. High efficacy was found with olopatadine and ebastine (VAS score = 7.0). Similar high efficacy was observed in the first-generation antihistamine *d*-chlorpheniramine.

It is thought that the anti-sedative effect of antihistamines depends on how easily they cross the blood-brain barrier. It also depends on their lipophilicity, molecular size, ion state, and affinity for P-glycoprotein, an efflux pump expressed in the blood-brain barrier of the antihistamines.[19-21] Yanai *et al*., classified H_1 antihistamines into three categories, non-sedative, less-sedative, and sedative by measuring H1R occupancy using positron emission tomography (PET) with [^{11}C]doxepin.[3-7] The H1R occupancies of the first-generation antihistamines showed over 50% and confirmed their easy penetration into the blood-brain barrier. The H1R occupancies of the second-generation antihistamines are calculated as 0–30%, and antihistamines of which H1R occupancy is less than 20%, such as olopatadine, ebastine, and fexofenadine are classified into the non-sedative group.[7] Hindmarch *et al*., classified the second-generation antihistamines into two groups according to proportional impairment ratios (PIR) by meta-analysis.[8,9] They also classified fexofenadine and ebastine as a non-sedative group.[8] Strong correlation was found (r = 0.723) between H1R occupancy and PIR (Fig. 5C).

The degree of sleepiness of the H_1 antihistamines by VAS analysis showed a strong correlation with PIR (r = 0.764, Fig. 5A) and moderate correlation with H1 R occupancy (r = 0.661, Fig. 5B). According to the data from both PET studies and meta-analysis, fexofenadine is considered as a non-sedative antihistamine. However, in VAS analysis, it showed similar sedative effects as epinatine and loratadine (Fig. 4). By the PET studies and meta-analysis, ebastine was also classified as a non-sedative antihistamine and cetirizine and mequitazine as less-sedative antihistamines. But, the mean value of sleepiness of ebastine was same as those of cetirizine and mequitazine in the VAS analysis. The H1R occupancy of olopatadine was calculated as 15% and it was classified as a non-sedative antihistamine by the PET study. However, olopatadine showed a high VAS score, the same as that of the first-generation antihistamine clemastine in sleepiness. The observation that patients taking olopatadine feel sleepy even though it does not penetrate into the blood-brain barrier readily (Fig. 4) suggests the existence of an unknown mechanism in sedation by olopatadine. Similar sedative effects of olopatadine were previously reported.[22]

H_1 antihistamines, especially the first-generation antihistamines, induce sedation, and thereby can cause life-threatening problems for patients even at recommended doses. Thus it is important to evaluate the properties of the sedative effect of H_1 antihistamines. As reported in numerous studies, H1R occupancy and PIR are thought to be useful tools for this purpose. However, PET apparatus are not available everywhere and it is not easy to collect enough data in a short time. Also calculation of PIR is not easy because all previous reports on sedation caused by H_1 antihistamines have to be reviewed.[8] On the other hand, VAS analysis using simple questionnaires is very easy for patients to answer and a large number of data can be easily collected. Our results of the evaluation of sleepiness by H_1 antihistamines by VAS analysis were very similar to that of H1R occupancy by PET studies and PIR by meta-analysis. This indicates that large-scale surveillance using VAS might be useful to evaluate the profiles of H_1 antihistamines.

ACKNOWLEDGEMENTS

We thank Drs Asish Kumar Das and Chieko Kakutani for help in manuscript preparation. This work was financially supported by Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (18390167 to H.F.) and by a fund from the Osaka Medical Research Foundation for Incurable Diseases.

REFERENCES

1. Goldberg MJ, Spector R, Chiang CK. Transport of diphenhydramine in the central nervous system. *J Pharmacol Exp Ther* 1987;**240**:717-22.
2. Adelsberg BR. Sedation and performance issues in the treatment of allergic conditions. *Arch Intern Med* 1997; **157**:494-500.
3. Yanai K, Ryu JH, Watanabe T *et al*. Positron emission tomographic study of central histamine H1-receptor occupancy in human subjects treated with epinastine, a second-generation antihistamine. *Methods Find Exp Clin Pharmacol* 1995;**17**:64-9.
4. Yanai K, Ryu JH, Watanabe T *et al*. Histamine H1 receptor occupancy in human brain after single oral dose of histamine H1 antagonists measured by positron emission tomography. *Br J Pharmacol* 1995;**116**:1649-55.
5. Yanai K, Okumura N, Tagawa M, Itoh M, Watanabe T. New findings in pharmacological effects induced by antihistamines: from PET studies to knock-out mice. *Clin Exp Allergy* 1999;**29**:29-36; discussion 37-8.
6. Tagawa M, Kano M, Okumura N *et al*. Neuroimaging of histamine H1-receptor occupancy in human brain by positron emission tomography (PET): a comparative study of ebastine, a second-generation antihistamine, and (+)-chlorpheniramine, a classical antihistamine. *Br J Clin Pharmacol* 2001;**52**:501-9.
7. Yanai K, Tashiro M. The physiological and pathophysi-

ological roles of neuronal histamine: An insight from human positron emission tomography studies. *Pharmacol Ther* 2007;**113**:1-15.
8. Shamsi Z, Hindmarch I. Sedation and antihistamines: a review of inter-drug differences using proportional impairment ratios. *Hum Psychopharmacol* 2000;**15**:S3-S30.
9. Hindmarch I, Shamsi Z, Kimber S. An evaluation of the effects of high-dose fexofenadine on the central nervous system: a double-blind, placebo-controlled study in healthy volunteers. *Clin Exp Allergy* 2002;**32**:133-9.
10. Femandez E, Turk DC. Sensory and affective components of pain: separation and synthesis. *Psychol Bull* 1992;**112**: 205-17.
11. Fries JF, Spitz PW, Young DY. The dimensions of health outcomes: the health assessment questionnaire, disability and pain scale. *J Rheumatol* 1982;**9**:189-96.
12. Ehrs PO, Berg H, Larsson K. Quality of life in primary care asthma. *Respir Med* 2001;**95**:22-30.
13. Ng KH, Chong D, Wong CK *et al*. Central nervous system side effects of first- and second-generation antihistamines in school children with perennial allergic rhinitis: a randomized, double-blind, placebo-controlled comparative study. *Pediatrics* 2004;**113**:116-21.
14. Brown RE, Stevens DR, Haas HL. The physiology of brain histamine. *Prog Neurobiol* 2001;**63**:637-72.
15. Haas H, Panula P. The role of histamine and the tuberomamillary nucleus in the nervous system. *Nat Rev Neurosci* 2003;**4**:121-30.
16. Eigenmann PA, Zamora SA. An internet-based survey on the circumstances of food-induced reactions following the diagnosis of IgE-mediated food allergy. *Allergy* 2002;**57**: 449-53.
17. Uguz A, Lack G, Pumphrey R *et al*. Allergic reactions in the community: a questionnaire survey of members of the anaphylaxis campaign. *Clin Exp Allergy* 2005;**35**:746-50.
18. Assanasen P, Naclerio RM. Antiallergic anti-inflammatory effects of H1-antihistamines in humans. *Clin Allergy Immunol* 2002;**17**:101-39.
19. Drescher S, Schaeffeler E, Hitzl M *et al*. MDR1 gene polymorphism and disposition of the P-glycoprotein substrate fexofenadine. *Br J Clin Pharmacol* 2002;**53**:526-34.
20. Del Cuvillo A, Mullol J, Bartra J *et al*. Comparative pharmacology of the H_1 antihistamines. *J Investig Allergol Clin Immunol* 2006;**16**:3-12.
21. Simons FE, Simons KJ. The pharmacology and use of H1-receptor-antagonist drugs. *N Engl J Med* 1994;**330**:1663-70.
22. Takahashi H, Ishida-Yamamoto A, Iizuka H. Effects of bepotastine, cetirizine, fexofenadine, and olopatadine on histamine-induced wheal-and flare-response, sedation, and psychomotor performance. *Clin Exp Dermatol* 2004; **29**:526-32.