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Dose dependency of brain histamine H1 receptor occupancy following oral administration of cetirizine hydrochloride measured using PET with [^{11}C]doxepin

Manabu Tashiro[1]*, Motohisa Kato[3], Masayasu Miyake[1], Shoichi Watanuki[1], Yoshihito Funaki[2], Yoichi Ishikawa[2], Ren Iwata[2] and Kazuhiko Yanai[1,3]

[1]*Divisions of Cyclotron Nuclear Medicine, Cyclotron and Radioisotope Center, Tohoku University, Sendai, Miyagi, Japan*
[2]*Divisions of Radiopharmaceutical Chemistry, Cyclotron and Radioisotope Center, Tohoku University, Sendai, Miyagi, Japan*
[3]*Department of Pharmacology, Tohoku University Graduate School of Medicine, Sendai, Miyagi, Japan*

Aims The strength of sedation due to antihistamines can be evaluated using positron emission tomography (PET). The purpose of the present study is to measure histamine H_1 receptor (H_1R) occupancy following oral administration of cetirizine (10 and 20 mg) in order to examine dose dependency.
Methods Fifteen healthy male volunteers (age range, 20–35 years) were divided into 3 subgroups and were studied following single oral administration of cetirizine at 10 mg ($n = 5$) and 20 mg ($n = 5$) or hydroxyzine at 30 mg ($n = 5$) using PET with ^{11}C-doxepin. Each subject was scanned also following the administration of placebo. Binding potential and H_1RO values were calculated in the prefrontal and anterior cingulate cortices. Subjective sleepiness was also measured, and the correlation to H_1RO was examined for each antihistamine.
Results The averaged H_1ROs of cetirizine 10 mg, 20 mg, and hydroxyzine 30 mg in the prefrontal and cingulate cortices was 12.6%, 25.2%, and 67.6%, respectively. The H_1RO of hydroxyzine 30 mg correlated well with subjective sleepiness ($p < 0.001$); however, those of cetirizine 10 and 20 mg showed no correlation with subjective sleepiness.
Conclusion It was demonstrated that the brain penetration of orally administered cetirizine was dose-dependent. Cetirizine 10 mg, with its low H_1RO and thus minimal sedation, could be more safely used than cetirizine 20 mg for the treatment of various allergic disorders.

KEY WORDS — cetirizine; hydroxyzine; histamine H_1 receptor (H_1R); histamine H_1 receptor occupancy (H_1RO); positron emission tomography (PET); binding potential; sedation

INTRODUCTION

Histamine H_1 receptor (H_1R) antagonists commonly known as antihistamines are often used for the treatment of allergic disorders such as seasonal rhinitis. Antihistamines act mainly on the peripheral tissues but can also induce sedation as a central side effect. This undesirable side effect is caused by blockade of nerve transmission in the histaminergic neuronal system. This system projects from the tuberomammillary nucleus in the posterior hypothalamus to almost all cortical areas (Casale et al., 2003; Haas and Panula, 2003; Holgate et al., 2003). First-generation (sedative) antihistamines that can easily penetrate the blood-brain barrier (BBB), such as d-chlorpheniramine and hydroxyzine, tend to occupy a large proportion of post-synaptic H_1Rs (more than 50%) (Yanai et al., 1995a; Yanai et al., 1995b; Yanai et al., 1999; Okamura et al., 2000; Tagawa et al., 2001; Van Hoecke et al., 2007). Mildly-sedative antihistamines, such as cetirizine and terfenadine, slightly penetrate the BBB and mildly occupy H_1Rs in the brain (usually not more than 20% or so). Moreover, they tend to induce slight sedation at low or recommended doses, but cause dose-related cognitive impairment at higher doses. Non-sedative antihistamines (e.g., fexofenadine), which have recently been introduced as an additional subcategory, can hardly penetrate the BBB and sparingly occupy H_1Rs. Since they do not penetrate the BBB easily, they induce no sedation even at exceeded doses (Hindmarch et al., 2002; Casale et al., 2003; Holgate et al., 2003; Van Hoecke et al., 2007). We previously demonstrated the difference in BBB

* Correspondence to: Dr M. Tashiro, Division of Cyclotron Nuclear Medicine, Cyclotron and Radioisotope Center, Tohoku University, Aoba 6-3, Aramaki, Aoba-ku, Sendai, Miyagi 980-8578, JAPAN, Tel: +81-22-795-7797 Fax: +81-22-795-7797, Japan.
E-mail: mtashiro@m.tains.tohoku.ac.jp

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permeability between mildly-sedative and non-sedative antihistamines using positron emission tomography (PET) and [^{11}C]doxepin following oral administration of double doses of cetirizine (20 mg) and fexofenadine (120 mg) (Tashiro et al., 2004). Thus, variation in cerebral H_1R occupancy (H_1RO) of antihistamines can be evaluated in terms of ''BBB permeability'' using PET and [^{11}C]doxepin.

It is of great social importance to note that users of mildly-sedative antihistamines tend to be less cautious and might take these drugs at double or triple doses when the desired effects are not achieved by the recommended doses even while driving a car or operating potentially dangerous machinery (Casale et al., 2003; Haas and Panula, 2003; Holgate et al., 2003). It is therefore important to examine the dose dependency of mildly-sedative antihistamines since no study has been available to date regarding the comparison of H_1ROs following treatment with these antihistamines at different doses. The primary aim of the present study is to compare the H_1ROs of cetirizine at 10 and 20 mg using PET, as well as to examine such cetirizine H_1ROs against that of hydroxyzine at 30 mg, a typical sedative antihistamine.

METHODS

The present study was approved by the Committee on Clinical Investigation of the Tohoku University Graduate School of Medicine and by the Institutional Review Committee of the Cyclotron and Radioisotope Center, Tohoku University, Sendai, Japan, and was performed in accordance with the policy of the declaration of Helsinki.

Subjects and study design

Fifteen male Japanese volunteers (age range, 20–35 years), recruited through an advertisement as study subjects, were provided with a clear description of the study, and their written informed consents were obtained. All the subjects were in good health with no clinical history of major physical or mental illnesses, and were also not receiving any concomitant medication likely to interfere with the study results. There were no abusers of alcohol, caffeine, or nicotine. Alcohol, nicotine, caffeine, grapefruit, and grapefruit juice were forbidden during the study period, and food intake was controlled on the test day and the day before PET measurement. The volunteers were requested to finish a light meal at least 3 h before the start of the study.

Out of the 15 subjects, each of five subjects was administered cetirizine at 10 mg (CET10 group: mean age +/- S.D. = 21.6 +/− 1.5 y.o.; mean body weight [BW] = 60.8 +/− 7.1 kg), cetirizine at 20 mg (CET20 group: mean age +/- S.D. = 23.2 +/− 1.1 y.o.; mean BW = 60.8 +/− 5.4 kg), and hydroxyzine at 30 mg (HYD group: mean age +/- S.D. = 23.2 +/− 0.8 y.o.; mean BW = 63.6 +/− 8.6 kg). Each subject underwent PET measurements after single oral administration of one of the above antihistamines or placebo (i.e., lactobacteria preparation, 6 mg), with minimum washout intervals of 7 days between treatments. Active and placebo conditions were cross-randomized in the present study. Lactobacteria preparation has been widely used as placebo in Japan, and has shown no statistical difference between pre- and post-administration in our previous cognitive studies (Okamura et al., 2000; Tagawa et al., 2002; Tashiro et al., 2004).

Measurement of subjective sleepiness

In each subject, subjective sleepiness was measured using the line analogue rating scale (LARS) (Parkin et al., 1998; Shamsi et al., 2001) at pre-administration and 0.5, 1, 1.5, 2, 2.5, and 3 h post-administration of each antihistamine or placebo. For each antihistamine condition, the measured subjective sleepiness was compared with that following placebo administration (Figure 1).

PET tracer and image acquisition

[^{11}C]doxepin was prepared by [^{11}C]methylation of desmethyl doxepin with [^{11}C]methyl triflate, as described previously (Iwata et al., 2001). The radiochemical purity of [^{11}C]doxepin was more than 99%, and its specific radioactivity at the time of injection was 64.9 +/− 45.3 GBq/μmol (1.75 +/− 1.23 Ci/μmol). [^{11}C]doxepin-containing saline solution was intravenously injected to each subject at 90 min after oral administration of the antihistamines, which was nearly similar to the known T_{max} of each antihistamine used: 2.1 +/−0.4 h for hydroxyzine in healthy Caucasoids, and 1.4 +/− 0.5 for CET 10 mg and 1.5 +/− 0.4 for 20 mg in Japanese volunteers (Simons et al., 1984; Lefebvre et al., 1988; Sasa et al., 1995; Tashiro et al., 2004). The injected dose and cold mass of [^{11}C]doxepin were 143.2 +/− 40.8 MBq (3.87 +/− 1.10 mCi), and 3.65 +/− 2.80 nmol, respectively.

Shortly before [^{11}C]doxepin injection, the subjects were positioned on the coach of the PET scanner so that

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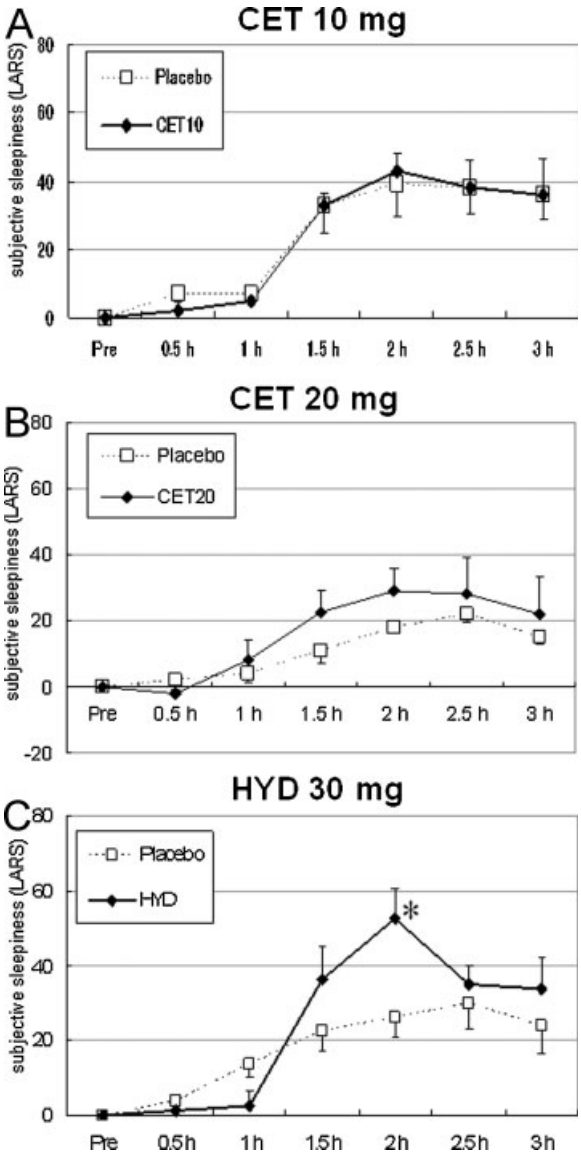

Figure 1. Results of measurements of subjective sleepiness following oral administration of cetirizine (10 and 20 mg), and hydroxyzine (30 mg). Each graph indicates the time-course of subjective sleepiness measured using the line analogue rating scale (LARS) at pre-administration and 0.5, 1, 1.5, 2, 2.5, and 3 h post-administration. Following cetirizine (10 mg) administration, there was no significant difference compared with following placebo administration (A). Following cetirizine (20 mg) administration, there was a trend for increased sleepiness, but a significant difference was not shown relative to the placebo condition (B). Following hydroxyzine (30 mg) administration, there was a significant increase in sleepiness compared with the placebo condition (C). Abbreviations: Pre = pre-administration, CET10 = cetirizine 10 mg, CET20 = cetirizine 20 mg, HYD = hydroxyzine

the transaxial slices were parallel to the orbitomeatal line. Subjects taking cetirizine at 10 and 20 mg were scanned using SET-2400W (Shimadzu Co., Kyoto, Japan), and those taking hydroxyzine at 30 mg were scanned using ECAT PT931 (CTI, Inc., Knoxville, TN, USA). Further details regarding these scanners were described in our previous reports (Fujiwara et al., 1997; Tashiro et al., 2004). Following transmission scan using the $^{68}Ge/^{68}Ga$ line source for tissue attenuation correction, the subjects were then scanned to detect emission of high-energy photons (511 keV) (emission scan). After tissue attenuation correction and reconstruction with a filtered back-projection algorithm, the brain images were processed by applying graphical analysis to obtain binding potential (BP) images (Logan et al., 1990; Logan et al., 1996) using the time–activity curve in the cerebellum based on region of interest (ROI) analysis. This method was previously validated and described in detail (Suzuki et al., 2005). Finally, H_1RO was calculated based on the BP values of the frontal cortex and cingulate gyrus, where the H_1R density was the highest and the most suitable for H_1RO calculation. The H_1ROs of antihistamines were calculated based on the following equation: $H_1RO = [(BP \text{ with placebo} - BP \text{ with given antihistamine}) / BP \text{ with placebo}] \times 100$.

Statistical analysis. Differences in H_1ROs between cetirizine (10 and 20 mg) and hydroxyzine (30 mg) were examined using one-way ANOVA with Bonferroni correction for multiple comparisons. The relationship between plasma drug concentration and H_1RO was examined using Pearson's correlation test. A probability of $p < 0.05$ was considered statistically significant. All statistical examinations were performed using SPSS for Windows 15.0 (Japanese version). For correlation analysis between H_1RO and subjective sleepiness, we have calculated the ''LARS_AUC ratio'' by taking the ratio of AUC curves of subjective sleepiness (LARS) following an antihistamine treatment to that following placebo treatment, in order to normalize inter-individual differences of subjective sleepiness. And correlation was examined between H_1RO and subjective sleepiness.

RESULTS

Subjective sleepiness

Results of subjective sleepiness measurements using LARS are shown in Figure 1. Subjective sleepiness following cetirizine 10 mg administration was not significantly different compared with that following placebo administration (Figure 1A). Following cetirizine 20 mg administration, a trend for increased sleepiness was observed, but this increase showed no

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Table 1. Binding potential and histamine H_1 receptor occupancy following administration of antihistamines and placebo

Drug and Region	BP (S.E.M.)	BP_{Pla} (S.E.M.)	H_1RO [%](S.E.M.)
Hydroxyzine (30 mg)	BP_{HYD}	BP_{Pla}	H_1RO_{HYD}
frontal	0.15 (0.06)	0.53 (0.07)	64.4 (9.1)
cingulate	0.24 (0.03)	0.67 (0.02)	70.7 (5.8)
Cetirizine (20 mg)	BP_{CET20}	BP_{Pla}	H_1RO_{CET20}
frontal	0.44 (0.09)	0.62 (0.11)	25.5 (9.5)
cingulate	0.50 (0.04)	0.66 (0.05)	24.8 (6.5)
Cetirizine (10 mg)	BP_{CET10}	BP_{Pla}	H_1RO_{CET10}
frontal	0.54 (0.04)	0.62 (0.05)	11.6 (3.3)
cingulate	0.68 (0.03)	0.78 (0.02)	13.6 (3.4)

significant difference compared with the placebo condition (Figure 1B). After hydroxyzine 30 mg administration, a significant increase in sleepiness was observed compared with the placebo condition (Figure 1C).

ROI-based comparison of BP and H_1RO

BP values in H_1R-rich regions such as the frontal and cingulate cortices were evaluated based on ROI analysis (Table 1 and Figure 2). BP values following treatment with cetirizine 10 mg were only slightly lower than that following placebo treatment in the same subjects. However, BP values following treatment with hydroxyzine 30 mg were considerably low compared with those following placebo treatments. BP values after treatment with cetirizine 20 mg were between those following treatments with cetirizine 10 mg and hydroxyzine 30 mg (Table 1).

H_1ROs following treatment with cetirizine (10 and 20 mg) and hydroxyzine (30 mg) were also calculated using the BP following antihistamine treatment in each subject and utilizing the BP data following placebo treatment in each subject as baseline (0%) (Table 1, Figure 2). The mean H_1ROs of the frontal and cingulate cortices following treatment with cetirizine 10 mg were 11.6 and 13.6%, respectively (average, 12.6%). Those following treatment with cetirizine 20 mg were 25.5 and 24.8%, respectively (average, 25.2%). Those following treatment with hydroxyzine 30 mg were 64.4 and 70.7%, respectively (average, 67.6%). These results show that H_1RO following treatment with hydroxyzine is substantially higher than that following treatment with cetirizine (Table 1, Figure 2). The differences in both the cetirizine groups to the hydroxyzine group were statistically significant (Figure 2).

As for the correlation between H_1RO and subjective sleepiness, the significant positive correlation was observed with hydroxyzine in the frontal cortex ($r = 0.91$, $p = 0.034$) but not in the cingulate cortex ($r = 0.76$, $p = 0.14$), respectively (Figure 3). A trend for positive correlation was observed with cetirizine 20 mg, although the correlation was not significant in neither the cingulate ($r = 0.68$, $p = 0.21$) nor frontal ($r = -0.74$, $p = 0.15$) (Figure 3). As for cetirizine 10 mg, H_1RO and subjective sleepiness were inconsistent, demonstrating trends for positive correlation in the cingulate cortex ($r = 0.47$, $p = 0.43$) and negative

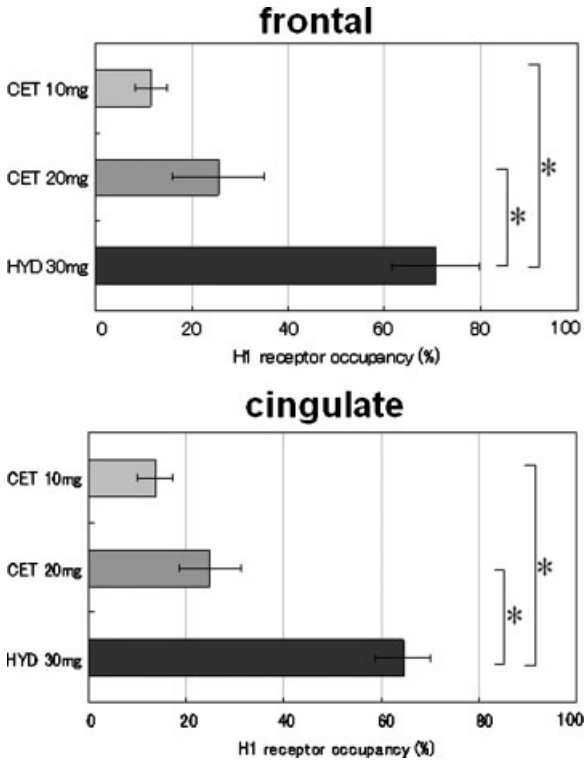

Figure 2. Histamine H_1 receptor occupancy (H_1RO) in the cingulate and frontal cortices. ROI measurements were performed in the anterior cingulate and frontal cortices following oral administration of cetirizine (10 and 20 mg) and hydroxyzine (30 mg). H_1RO due to these antihistamines are shown, taking H_1RO by those under the placebo condition as 0%. H_1RO of hydroxyzine following administration was significantly higher than those of the other antihistamines. * $p < 0.001$, ANOVA followed by the Bonferroni test for multiple comparison. Error bars represent inter-individual variability (S.E.M.). Abbreviations: CET10mg = cetirizine 10 mg, CET20 mg = cetirizine 20 mg, HYD30 mg = hydroxyzine 30 mg

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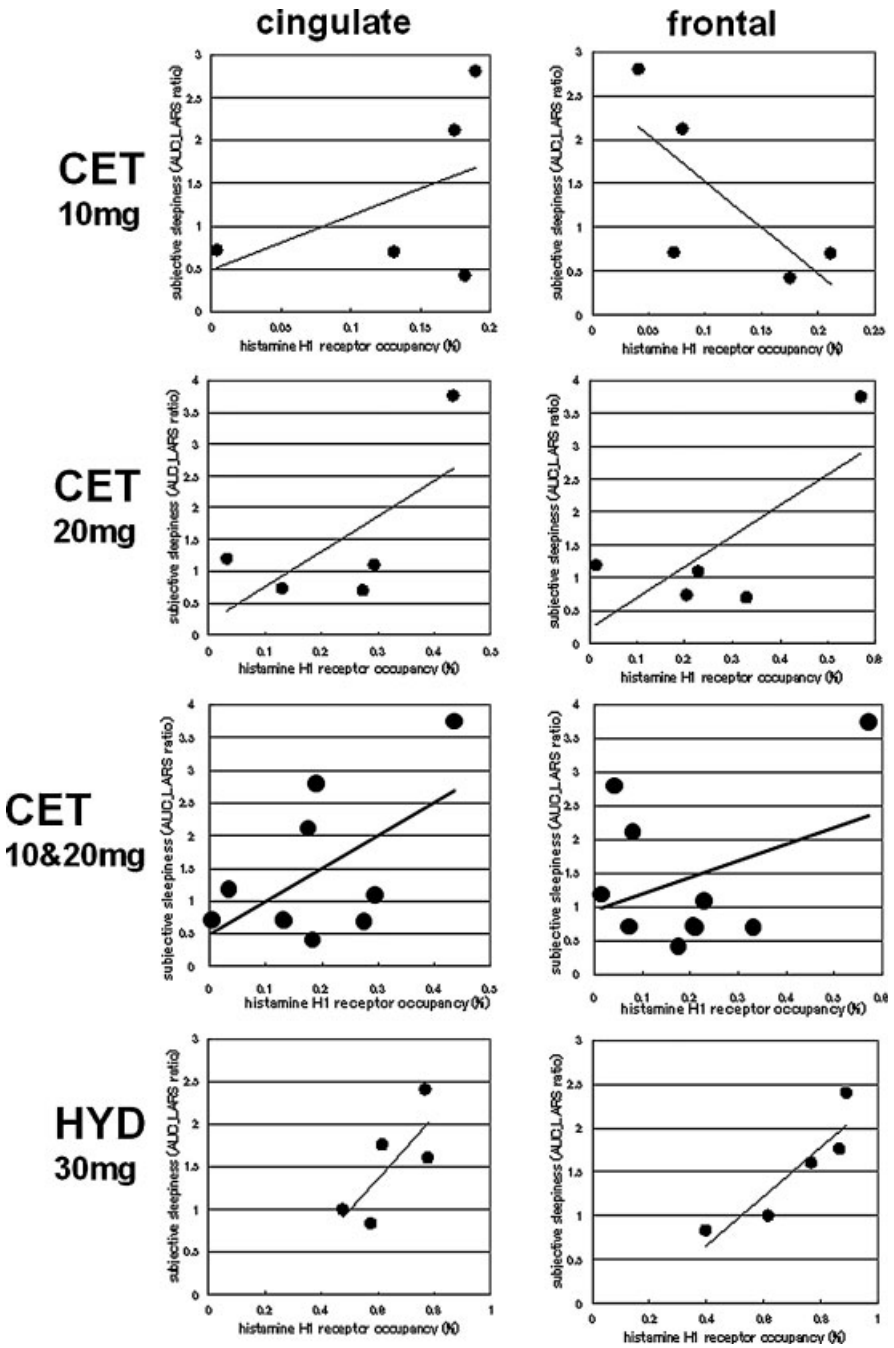

Figure 3. Correlation between histamine H1 receptor occupancy (H_1RO) and subjective sleepiness in the cingulate and frontal cortices. Subjective sleepiness is indicated as the ratio of area under the curves for the 3 h-long follow-up data of line analogue rating scale (LARS) following oral administration of each antihistamine and placebo. Abbreviations: CET10mg = cetirizine 10 mg, CET20mg = cetirizine 20 mg, CET10&20 mg = cetirizine 10 and 20 mg, HYD 30mg = hydroxyzine 30 mg

correlation in the frontal cortex ($r = -0.73$, $p = 0.16$), though both were insignificant (Figure 3). When cetirizine 10 and 20 mg data were plotted together, a trend for positive correlation was observed in the cingulate ($r = 0.58$, $p = 0.08$) but not in the frontal regions ($r = 0.36$, $p = 0.30$) (Figure 3).

DISCUSSION

In the present study, the H_1RO of cetirizine, a mildly-sedative antihistamine, was compared between two doses of 10 and 20 mg in a single-blinded placebo-controlled study design. Moreover, the H_1RO of

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hydroxyzine 30 mg, a typical sedative antihistamine, was also calculated. In previous research, we calculated the H_1RO of oral cetirizine 20 mg; however, the investigation was not a placebo-controlled study. This means that the control data used for calculating H_1ROs were obtained from different subjects with the aim of reducing radiation exposure to subjects (Tashiro et al., 2004). In addition, the H_1RO of hydroxyzine was not measured in that previous study. Thus, an additional aim of the present study was to measure the H_1RO of hydroxyzine at 30 mg. The placebo-controlled study design required at least two scans for each subject and for each drug, and the use of the three-dimensional (3D) data acquisition mode enabled the reduction of radiation exposure (mean +/- S.D.: 1.98 +/− 0.57 mSv), that is, considerably smaller than that in our previous study using the 2D data acquisition mode (average, 4.31 mSv) (Tashiro et al., 2004). Therefore, the 3D data acquisition mode is suitable for conducting placebo-controlled PET clinical trials.

In the present study, we found that the baseline BP under the placebo condition showed a certain inter-individual variation (the mean values under the placebo condition for the subgroups of cetirizine 10 and 20 mg and hydroxyzine 30 mg were 0.62 +/− 0.05, 0.62 +/− 0.11, and 0.53 +/− 0.07, respectively)(Table 1). This result suggests the use of a placebo-controlled study design could minimize the effect of inter-individual variation, although the H_1RO of cetirizine 20 mg in this placebo-controlled study (mean value of frontal and cingulate cortices, 25.2%) was slightly different from that obtained in our previous study (mean value of frontal and cingulate cortices. 28.9%) (Tashiro et al., 2004).

It has been known that sedative antihistamines, such as hydroxyzine, ketotifen, diphenhydramine, and d-chlorpheniramine, occupy more than 50% of available H_1Rs, resulting in high prevalence of sleepiness and cognitive decline (Yanai et al., 1995a; Okamura et al., 2000; Tagawa et al., 2001; Tashiro et al., 2006; Van Hoecke et al., 2007; Tashiro et al., 2008). Hydroxyzine is a typical sedative antihistamine that induces psychomotor impairment even at recommended doses (20–30 mg), and it has been used as a positive control in many studies (Gengo et al., 1987; Gengo and Gabos, 1987; Walsh et al., 1992; Lee and Maibach, 2001; Van Hoecke et al., 2007). Cetirizine, also used in this study, is the main metabolite of hydroxyzine, and the conversion from hydroxyzine to cetirizine is mediated by alcohol dehydrogenase (Whomsley et al., 2005). In the present study, subjective sleepiness in the hydroxyzine group was significantly increased compared with the placebo condition, while the cetirizine subgroups did not show significant difference from the placebo conditions (Figure 1). In addition, H_1ROs following hydroxyzine treatment showed a significant difference relative to those following cetirizine treatment (Figure 2).

Mildly-sedative antihistamines, including cetirizine and loratadine, are regarded as less impairing and sedating than sedative antihistamines. For example, cetirizine at the recommended doses of 5–10 mg has been evaluated as being either non-sedating (Gengo et al., 1987; Gengo et al., 1990; Walsh et al., 1992; Patat et al., 1995; Hindmarch et al., 2001; Shamsi et al., 2001; Curran et al., 2004; Van Hoecke et al., 2007; Takahashi et al., 2008) or mildly sedating (Ramaekers et al., 1992; Bonifazi et al., 1995; Vermeeren et al., 2002). These results from the use of cetirizine are variable; at higher than the recommended doses (20 mg), the agent has been reported to produce significant drowsiness (Gengo and Gabos, 1987) and impairment in a selected task (Gengo et al., 1990) in some studies or no cognitive impairment (Gengo et al., 1987; Gengo and Gabos, 1987) in other investigations. In a recent meta-analysis (Hindmarch and Shamsi, 1999; Shamsi and Hindmarch, 2000), the proportional impairment ratios (PIRs) based on objective measurements were 0.18 and 2.25 for cetirizine and hydroxyzine, respectively. The PIRs based on subjective measures were 0.33 and 2.57 for cetirizine and hydroxyzine, respectively (Hindmarch and Shamsi, 1999), where a smaller PIR corresponds to a weaker sedative effect.

Therefore, it has been thought that second generation antihistamines are less impairing for use in day-to-day activities (Mattila and Paakkari, 1999; Tashiro et al., 2004; Theunissen et al., 2004). However, the strength of sedation seems to vary among users and further investigations have demonstrated that not all second generation antihistamines manifest similar ''non-sedative'' profiles. Recently, second generation antihistamines have been further classified into the following two subgroups (Casale et al., 2003; Holgate et al., 2003): those inducing slight sedation at low doses, but causing dose-related cognitive impairment at higher doses (''mildly-sedative'' antihistamines, e.g., cetirizine), and those inducing no sedation even at exceeded doses (''non-sedative'' antihistamines, e.g., fexofenadine) (Tashiro et al., 2004). Based on this classification, we previously compared the BBB permeability of cetirizine 20 mg and fexofenadine 120 mg (both doses were double the standard oral doses

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in Japan) in terms of H_1ROs. The results showed that the H_1ROs of both drugs were 26 and 0%, respectively (Tashiro et al., 2004). The H_1RO of 26% (mean value for the whole brain) was relatively high for a mildly-sedative antihistamine, suggesting that cetirizine might show dose-related brain penetration. This has been the rationale for conducting the present study in order to investigate whether dose-related BBB penetration is present or not. Examining the dose dependency of mildly-sedative antihistamines is also of great social importance because of overcompliance as mentioned in the introduction section. Comparison of H_1ROs following the oral administration of cetirizine 10 and 20 mg indicated clear dose-dependency in H_1ROs (Table 1 and Figure 2), although the difference was not statistically significant (Figure 2).

Variation in the BBB permeability among different antihistamines can be explained by various factors such as lipophilicity, molecular size, and different actions of drug transporters including a P-glycoprotein (P-gp). This is an efflux pump expressed in capillary endothelial cells in the BBB (Tashiro et al., 2006). Many sedative antihistamines are often lipophilic and can be absorbed in full amount in the gut, and they can freely diffuse into the brain space. In the case of mildly-sedative antihistamines with reduced lipophilicity, both gut absorption and brain penetration are limited. For fexofenadine, a substrate of P-gp, both gut absorption and BBB permeability are highly reduced because of its low membrane permeability and high action of P-gp. For cetirizine, also a substrate of P-gp but probably to a lesser extent than fexofenadine, will allow a certain amount of BBB penetration (Chen et al., 2003; Molimard et al., 2004). Our recent study demonstrated that bepotastine 10 mg, a new mildly-sedative antihistamine produced in Japan, has a similar structure to that of cetirizine and its H_1RO is similar to that of cetirizine 10 mg (mean value of frontal and cingulate: cortices,12.1%) (Tashiro et al., 2008). It is interesting to mention that bepotastine's chemical structure resembles that of cetirizine and its membrane permeability is greater than that of fexofenadine (Ohashi et al., 2006).

In our previous healthy volunteer study ($n = 10$)(Tashiro et al., 2004), the plasma concentrations of hydroxyzine and cetirizine (a main metabolite) following oral administration (120 min post-administration) of hydroxyzine 30 mg was 20.0 +/− 9.3 ng/ml and 146.3 +/− 50.3 ng/ml, respectively, although these results were not presented in the paper. In addition, the plasma cetirizine concentration following cetirizine treatment (20 mg) was 489.0 +/− 118.8 ng/ml. These pharmaco-kinetic data may suggest that a large proportion of hydroxyzine molecules rapidly distributed from the plasma into the tissue compartment and relatively small part of hydroxyzine molecules is rapidly metabolized into cetirizine. And according to Simons and colleagues, the elimination half lives do not differ largely between hydroxyzine (29.3 +/− 10.1 h) and cetirizine (24.8 +/− 7.7 h)(Simons et al., 2008). It seems that the subjective sedation is not associated with the plasma cetirizine concentration, but is associated with the brain distribution (penetration) of hydroxyzine measured as H_1RO.

Interestingly, a significant correlation between H_1RO and subjective sleepiness was observed following treatment with hydroxyzine 30 mg, but not following the treatment with cetirizine (Figure 3). This result suggests that subjective sleepiness is not reliable for evaluating the level of sedation particularly for mildly-sedative antihistamines. Thus, measurement of H_1RO using PET seems to be promising as recommended by the consensus group on new generation antihistamines (CONGA) (Holgate et al., 2003). CONGA is responsible for summarizing the core measures regarding the evaluation of the sedative profiles of new generation antihistamines (Holgate et al., 2003).

Here, we should discuss the limitations of the present study. First, we did not find a good correlation between subjective sleepiness and H_1RO. This would be partly because of inter-individual differences in drug responses. Considering variation in the results of previous cognitive studies on cetirizine (Gengo and Gabos, 1987; Gengo et al., 1990; Ramaekers et al., 1992; Bonifazi et al., 1995; Vermeeren et al., 2002), cetirizine is possibly an agent with relatively large inter-individual difference in its sedation. For the future replication to evaluate dose dependency, it would be better to scan each subject under three conditions of CET10, 20 mg and placebo using the same PET scanner. Different scanners were used for different antihistamines in the present study, though both scans were respectively compared to the placebo data obtained by the same scanner. In the second point, we did not measure the plasma drug concentration and were not able to examine the direct relationship between plasma drug concentration and H_1RO. Future study should clarify this relationship as well.

In conclusion, we examined the H_1RO of cetirizine at different oral doses of 10 and 20 mg, and compared the results with those from the oral administration of hydroxyzine 30 mg. Cetirizine 10 mg occupied

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approximately 13% of available H_1Rs in the frontal brain (frontal and cingulate cortices), while cetirizine 20 mg occupied approximately 25% of H_1Rs, confirming that brain penetration of mildly-sedative antihistamines tends to be dose-dependent. In addition, it is noteworthy for users to know that oral administration of cetirizine 10 mg could be more safely used for the treatment of allergic disorders, while an increased dose (20 mg or more) could result in mild sedation.

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REFERENCES

Bonifazi F, Provinciali L, Antonicelli L, *et al*., 1995. Comparative study of terfenadine and cetirizine in hay fever: assessment of efficacy and central nervous system effects. *J Investig Allergol Clin Immunol* **5**: 40–46.

Casale TB, Blaiss MS, Gelfand E, *et al*., 2003. First do no harm: managing antihistamine impairment in patients with allergic rhinitis. *J Allergy Clin Immunol* **111**: S835–842.

Chen C, Hanson E, Watson JW, Lee JS. 2003. P-glycoprotein limits the brain penetration of nonsedating but not sedating H1-antagonists. *Drug Metab Dispos* **31**: 312–318.

Curran MP, Scott LJ, Perry CM. 2004. Cetirizine: a review of its use in allergic disorders. *Drugs* **64**: 523–561.

Fujiwara T, Watanuki S, Yamamoto S, *et al*., 1997. Performance evaluation of a large axial field-of-view PET scanner: SET-2400W. *Ann Nucl Med* **11**: 307–313.

Gengo FM, Dabronzo J, Yurchak A, Love S, Miller JK. 1987. The relative antihistaminic and psychomotor effects of hydroxyzine and cetirizine. *Clin Pharmacol Ther* **42**: 265–272.

Gengo FM, Gabos C. 1987. Antihistamines, drowsiness, and psychomotor impairment: central nervous system effect of cetirizine. *Ann Allergy* **59**: 53–57.

Gengo FM, Gabos C, Mechtler L. 1990. Quantitative effects of cetirizine and diphenhydramine on mental performance measured using an automobile driving simulator. *Ann Allergy* **64**: 520–526.

Haas H, Panula P. 2003. The role of histamine and the tuberomamillary nucleus in the nervous system. *Nat Rev Neurosci* **4**: 121–130.

Hindmarch I, Johnson S, Meadows R, Kirkpatrick T, Shamsi Z. 2001. The acute and sub-chronic effects of levocetirizine, cetirizine, loratadine, promethazine and placebo on cognitive function, psychomotor performance, and weal and flare. *Curr Med Res Opin* **17**: 241–255.

Hindmarch I, Shamsi Z. 1999. Antihistamines: models to assess sedative properties, assessment of sedation, safety and other side-effects. *Clin Exp Allergy* **29** (Suppl 3): 133–142.

Hindmarch I, Shamsi Z, Kimber S. 2002. 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* **32**: 133–139.

Holgate ST, Canonica GW, Simons FE, *et al*., 2003. Consensus Group on New-Generation Antihistamines (CONGA): present status and recommendations. *Clin Exp Allergy* **33**: 1305–1324.

Iwata R, Pascali C, Bogni A, Miyake Y, Yanai K, Ido T. 2001. A simple loop method for the automated preparation of (11C)raclopride from (11C)methyl triflate. *Appl Radiat Isot* **55**: 17–22.

Lee EE, Maibach HI. 2001. Treatment of urticaria. An evidence-based evaluation of antihistamines. *Am J Clin Dermatol* **2**: 27–32.

Lefebvre RA, Rosseel MT, Bernheim J. 1988. Single dose pharmacokinetics of cetirizine in young and elderly volunteers. *Int J Clin Pharmacol Res* **8**: 463–470.

Logan J, Fowler JS, Volkow ND, Wang GJ, Ding YS, Alexoff DL. 1996. Distribution volume ratios without blood sampling from graphical analysis of PET data. *J Cereb Blood Flow Metab* **16**: 834–840.

Logan J, Fowler JS, Volkow ND, *et al*., 1990. Graphical analysis of reversible radioligand binding from time-activity measurements applied to [N-11C-methyl]-(-)-cocaine PET studies in human subjects. *J Cereb Blood Flow Metab* **10**: 740–747.

Mattila MJ, Paakkari I. 1999. Variations among non-sedating antihistamines: are there real differences? *Eur J Clin Pharmacol* **55**: 85–93.

Molimard M, Diquet B, Benedetti MS. 2004. Comparison of pharmacokinetics and metabolism of desloratadine, fexofenadine, levocetirizine and mizolastine in humans. *Fundam Clin Pharmacol* **18**: 399–411.

Ohashi R, Kamikozawa Y, Sugiura M, Fukuda H, Yabuuchi H, Tamai I. 2006. Effect of P-glycoprotein on intestinal absorption and brain penetration of antiallergic agent bepotastine besilate. *Drug Metab Dispos* **34**: 793–799.

Okamura N, Yanai K, Higuchi M, *et al*., 2000. Functional neuroimaging of cognition impaired by a classical antihistamine, d-chlorpheniramine. *Br J Pharmacol* **129**: 115–123.

Parkin C, Fairweather DB, Shamsi Z, Stanley N, Hindmarch I. 1998. The effects of cigarette smoking on overnight performance. *Psychopharmacology (Berl)* **136**: 172–178.

Patat A, Perault MC, Vandel B, Ulliac N, Zieleniuk I, Rosenzweig P. 1995. Lack of interaction between a new antihistamine, mizolastine, and lorazepam on psychomotor performance and memory in healthy volunteers. *Br J Clin Pharmacol* **39**: 31–38.

Ramaekers JG, Uiterwijk MM, O'Hanlon JF. 1992. Effects of loratadine and cetirizine on actual driving and psychometric test performance, and EEG during driving. *Eur J Clin Pharmacol* **42**: 363–369.

Sasa M, Naito M, Kojima T. 1995. Pharmacokinetics of single and multiple doses of a new antiallergic drug, cetirizine, and examination of its safety. *Jpn J Clin Pharmacol Ther* **26**: 509–522.

Shamsi Z, Hindmarch I. 2000. Sedation and antihistamines: a review of inter-drug differences using proportional impairment ratios. *Hum Psychopharmacol* **15**: S3–S30.

Shamsi Z, Kimber S, Hindmarch I. 2001. An investigation into the effects of cetirizine on cognitive function and psychomotor performance in healthy volunteers. *Eur J Clin Pharmacol* **56**: 865–871.

Simons FE, Simons KJ, Frith EM. 1984. The pharmacokinetics and antihistaminic of the H1 receptor antagonist hydroxyzine. *J Allergy Clin Immunol* **73**: 69–75.

Simons K, Simons E, Whomsley R, Gillard M, Strolin-Benedetti M. 2008. Hydroxyzine and its active metabolite cetirizine: H1-receptor occupancy in healthy elderly adults. *Allergy* **63**: 541.

Suzuki A, Tashiro M, Kimura Y, *et al*., 2005. Use of reference tissue models for quantification of histamine H1 receptors in human brain by using positron emission tomography and [11c] doxepin. *Ann Nucl Med* **19**: 425–433.

Tagawa M, Kano M, Okamura N, *et al*., 2002. Differential cognitive effects of ebastine and (+)-chlorpheniramine in healthy subjects: correlation between cognitive impairment and plasma drug concentration. *Br J Clin Pharmacol* **53**: 296–304.

Tagawa M, Kano M, Okamura N, *et al*., 2001. Neuroimaging of histamine H1-receptor occupancy in human brain by positron emission tomography (PET): a comparative study of ebastine, a second-generation antihista-

mine, and (+)-chlorpheniramine, a classical antihistamine. *Br J Clin Pharmacol* **52**: 501–509.

Takahashi H, Zhang Y, Morita E. 2008. Evaluation of the antihistamine effects of olopatadine, cetirizine and fexofenadine during a 24 h period: a double-blind, randomized, crossover, placebo-controlled comparison in skin responses induced by histamine iontophoresis. *Arch Dermatol Res.* **300**: 291–295.

Tashiro M, Duan X, Kato M, *et al*., 2008. Brain histamine H(1) receptor occupancy of orally administered antihistamines, bepotastine and diphenhydramine, measured by PET with (11)C-doxepin. *Br J Clin Pharmacol* **65**: 811–821.

Tashiro M, Mochizuki H, Sakurada Y, *et al*., 2006. Brain histamine H receptor occupancy of orally administered antihistamines measured by positron emission tomography with (11)C-doxepin in a placebo-controlled crossover study design in healthy subjects: a comparison of olopatadine and ketotifen. *Br J Clin Pharmacol* **61**: 16–26.

Tashiro M, Sakurada Y, Iwabuchi K, *et al*., 2004. Central effects of fexofenadine and cetirizine: measurement of psychomotor performance, subjective sleepiness, and brain histamine H1-receptor occupancy using 11C-doxepin positron emission tomography. *J Clin Pharmacol* **44**: 890–900.

Theunissen EL, Vermeeren A, van Oers AC, van Maris I, Ramaekers JG. 2004. A dose-ranging study of the effects of mequitazine on actual driving, memory and psychomotor performance as compared to dexchlorpheniramine, cetirizine and placebo. *Clin Exp Allergy* **34**: 250–258.

Van Hoecke H, Vandenbulcke L, Van Cauwenberge P. 2007. Histamine and leukotriene receptor antagonism in the treatment of allergic rhinitis: an update. *Drugs* **67**: 2717–2726.

Vermeeren A, Ramaekers JG, O'Hanlon JF. 2002. Effects of emedastine and cetirizine, alone and with alcohol, on actual driving of males and females. *J Psychopharmacol* **16**: 57–64.

Walsh JK, Muehlbach MJ, Schweitzer PK. 1992. Simulated assembly line performance following ingestion of cetirizine or hydroxyzine. *Ann Allergy* **69**: 195–200.

Whomsley R, Strolin-Benedetti M, Espie P, Usuki E, Wolff A, Baltes E. 2005. The conversion of hydroxyzine to cetirizine is mediated by alcohol dehydrogenase. *Drug Metab Rev* **37**: 390–391.

Yanai K, Okamura N, Tagawa M, Itoh M, Watanabe T. 1999. New findings in pharmacological effects induced by antihistamines: from PET studies to knock-out mice. *Clin Exp Allergy* **29** (Suppl 3): 29–36; discussion. 37–28.

Yanai K, Ryu JH, Watanabe T, *et al*., 1995a. 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* **17** (Suppl C): 64–69.

Yanai K, Ryu JH, Watanabe T, *et al*., 1995b. Histamine H1 receptor occupancy in human brains after single oral doses of histamine H1 antagonists measured by positron emission tomography. *Br J Pharmacol* **116**: 1649–1655.

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