Relationship Between Brain Histamine H1 Receptor Occupancy Subjective Sleepiness and Plasma Drug Concentration Following Oral Administtation of Antihistamines Bepotastine and Diphenhydramine

著者	Tashiro M, Duan X, Kato M, Miyake M, Watanuki S, Ishikawa Y, Funai Y, Iwata R, Itoh M, Yanai K
journal or publication title	CYRIC annual report
volume	2007
page range	81-85
year	2007
URL	http://hdl.handle.net/10097/44393

VIII. 1 Relationship Between Brain Histamine H_1 Receptor Occupancy, Subjective Sleepiness and Plasma Drug Concentration Following Oral Administration of Antihistamines Bepotastine and Diphenhydramine

Tashiro M.[1], Duan X.[1], Kato M.[3], Miyake M.[1], Watanuki S.[1], Ishikawa Y.[2], Funaki Y.[2], Iwata R.[2], Itoh M.[1], and Yanai K.[1,3]

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

Introduction

Histamine H_1 receptor (H_1R) antagonists, or antihistamines, are often used for treatment of allergic diseases such as atopic dermatitis and seasonal rhinitis (also called pollinosis or hay fever). Antihistamines mainly act on these allergic sites in the peripheral tissues but can induce "sedative" side effects that result in subjective sleepiness and impaired performance. These undesirable central side effects are caused by blockade of nerve transmission in the histaminergic neuron system projecting from the tuberomammillary nucleus to almost all cortical areas[1-3]. First-generation antihistamines such as diphenhydramine and d-chlorpheniramine can easily penetrate blood-brain barrier (BBB) and tend to occupy a large proportion of post-synaptic H_1Rs[4-6]. Second-generation antihistamines, such as fexofenadine, cetirizine and olopatadine, can slightly penetrate the BBB and H1Rs are slightly occupied as having been demonstrated using positron emission tomography (PET)[4,7-9]. Variation in cerebral H_1R occupancy (H_1RO) of antihistamines results mainly from their different BBB permeability. Thus, sedative property of antihistamines can be evaluated in terms of H_1RO measured with PET and [^{11}C]doxepin, a radiopharmaceutical that specifically binds to H1Rs.

Methods

The present study was approved by the Committee on Clinical Investigation at Tohoku University Graduate School of Medicine, Japan, and was performed in accordance

with the policy of the Declaration of Helsinki. All experiments were performed at the Cyclotron and Radioisotope Centre, Tohoku University. Eight healthy male volunteers (mean age +/- s.d.: 24.4 +/- 3.3 years old) were studied after single oral administration of bepotastine 10 mg, diphenhydramine 30 mg, or placebo, using PET with [^{11}C]doxepin in a crossover study-design. The bepotastine is a novel second-generation antihistamine developed in Japan (Fig. 1), and diphenhydramine was added to the present study as an active placebo[10]. PET brain images were reconstructed with a filtered back projection algorithm. These brain images were normalized by plasma radioactivity data at 10 min post-injection and normalized by the distribution volume (DV) values in the cerebellum to yield specific binding potential ratio images[11]. Then, H_1R occupancy values were calculated using placebo data, and were compared between bepotastine and diphenhydramine. During the study, subjective sleepiness of each subject was measured in each subject at 0, 60, 120 and 180 min post-administration using the Line Analogue Rating Scale (LARS). Plasma concentrations of bepotastine and diphenhydramine were also measured at 0, 60, 120 and 180 min post-administration using liquid chromatography/ tandem mass spectrometry (LC/MS/MS). The relationship between plasma drug concentration (AUC) and H1RO was examined using Pearson's correlation test. A probability of $p<0.05$ was considered statistically significant[10].

Results

Result of mean subjective sleepiness is shown in Fig. 2. Mean subjective sleepiness of diphenhydramine peaked at 120 to 180 min post-administration and that of bepotastine peaked at 120 min post-administration. It was demonstrated that subjective sleepiness following diphenhydramine administration was significantly stronger ($p< 0.001$) than those of both bepotastine and placebo at 120 and 180 min post-administration, and that of bepotastine was not significantly different from that of placebo (Fig. 2).

Results of mean plasma concentrations of bepotastine and diphenhydramine demonstrated that the peak mean plasma concentration of bepotastine ranged from 60 to 180 min post-administration. Mean plasma concentration of diphenhydramine was maximal from 120 to 180 min post-administration[10] (data not shown here).

Brain images following oral administration of bepotastine demonstrated slightly lower binding potential ratio in comparison to those following placebo, and images following diphenhydramine administration demonstrated significantly lower binding potential ratio in comparison to both placebo and bepotastine (Fig. 3). Overall cortical

mean H_1RO of bepotastine and diphenhydramine were 14.8% and 56.8%, respectively[10].

Regarding the results of correlation analysis, mean H_1RO due to diphenhydramine tended to increase rapidly with diphenhydramine concentration when the baseline data are plotted together (Fig. 4A), while that due to bepotastine gradually increased with bepotastine concentration (Figure 4B). H_1RO following bepotastine administration did not significantly correlate to subjective sleepiness (Fig. 4D), while the H_1RO following diphenhydramine administration significantly correlated to subjective sleepiness (Figure 4C).

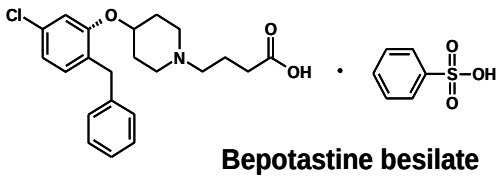
Discussion

To date, we have studied the mechanism of functional suppression in signal transmission through H_1Rs in the brain. In the present study, H_1RO of bepotastine, a second-generation antihistamine, was compared to that of diphenhydramine, a typical sedative antihistamine. H_1RO after a single oral administration of bepotastine 10 mg or diphenhydramine 30 mg was calculated as approximately 14.8% and 56.8%, respectively. Previous PET studies demonstrated that first-generation antihistamines occupied more than 50% of available H_1Rs and that the second-generation antihistamines would occupy around 0 to 20% of brain H_1Rs[4-6,9]. H_1RO after oral administration of bepotastine 10 mg was much lower than that of first-generation antihistamines (15% vs. 50%), and this result is in accordance with the categorization of bepotastine as a second-generation antihistamine. In addition, nowadays the second-generation antihistamines are further separated into 2 subgroups according to their BBB permeabilities[2,3]; a category that cause little sedation at low doses, but cause dose-related cognitive impairment at higher doses as seen with cetirizine and olopatadine, as well as the other category that does not cross BBB and therefore induces no sedation even at exceeded doses as seen with fexofenadine[9]. Based on the results of the present study, brain penetration of bepotastine has a certain level of dose dependency although subjective sleepiness is at a negligible level. The present results suggest that the bepotastine belongs to the category that causes little sedation at low doses but cause dose-related cognitive impairment at increased doses. The bepotastine demonstrated another cognitive study involving an active placebo is needed in order to draw a definitive conclusion. The dose dependency of H_1RO should also be examined by PET measurements at higher doses.

References

1) Haas H., Panula P., Nat. Rev. Neurosci. **4** (2003) 121.

2) Holgate ST., Canonica G.W., Simons F.E., et al., Clin. Exp. Allergy. **33** (2003) 1305.
3) Casale T.B., Blaiss M.S., Gelfand E., et al., J. Allergy Clin. Immunol. **111** (2003) S835.
4) Yanai K., Ryu J.H., Watanabe T., et al., Br. J. Pharmacol. **116** (1995) 1649.
5) Yanai K., Ryu J.H., Watanabe T., et al., Methods Find Exp. Clin. Pharmacol. **17** Suppl C(1995) 64.
6) Yanai K., Okamura N., Tagawa M., et al., Clin. Exp. Allergy. **29** Suppl 3 (1999) 29.
7) Okamura N., Yanai K., Higuchi M., et al., Br. J. Pharmacol. **129** (2000) 115.
8) Tagawa M., Kano M., Okamura N., et al., Br. J. Clin. Pharmacol. **52** (2001) 501.
9) Tashiro M., Sakurada Y., Iwabuchi K., et al., J. Clin. Pharmacol. **44** (2004) 8900.
10) Tashiro M., Duan X., Kato M., et al., Br. J. Clin. Pharmacol. **65** (2008) 811.
11) Mochizuki H., Kimura Y., Ishii K., et al., Nucl. Med. Biol. **31** (2004) 1005.



Bepotastine besilate

Figure 1. Chemical structure of bepotastine besilate.

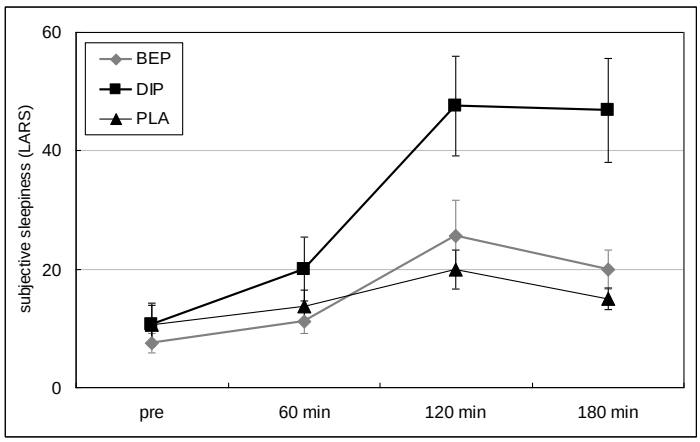


Figure 2. Subjective sleepiness evaluated using the Line Analogue Rating Scale (LARS). Eight healthy subjects were studied following oral administration of bepotastine (BEP, 10 mg), diphenhydramine (DIP, 30 mg), or placebo (PLA). *Reproduced from the reference [10] by courtesy of Blackwell Publishing Company.

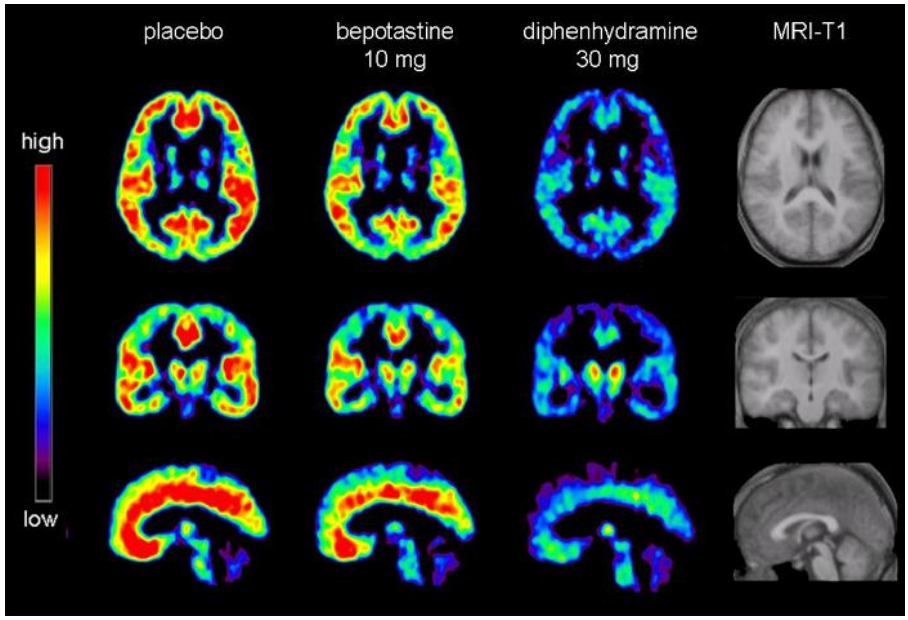


Figure 3. Binding potential ratio images of [^{11}C]doxepin in the human brain. Binding potential ratio of [^{11}C]doxepin was calculated in healthy male subjects (n=8) by PET following oral administrations of placebo (left), bepotastine (10 mg, middle) or diphenhydramine (30 mg, right) for each treatment condition were compared. White circles in the transaxial images indicate the regions of interest (ROIs). Brain image of each subject was transformed to fit stereotaxic brain space and was averaged across each drug condition to generate the mean images displayed here. *Reproduced from the reference [10] by courtesy of Blackwell Publishing Company.

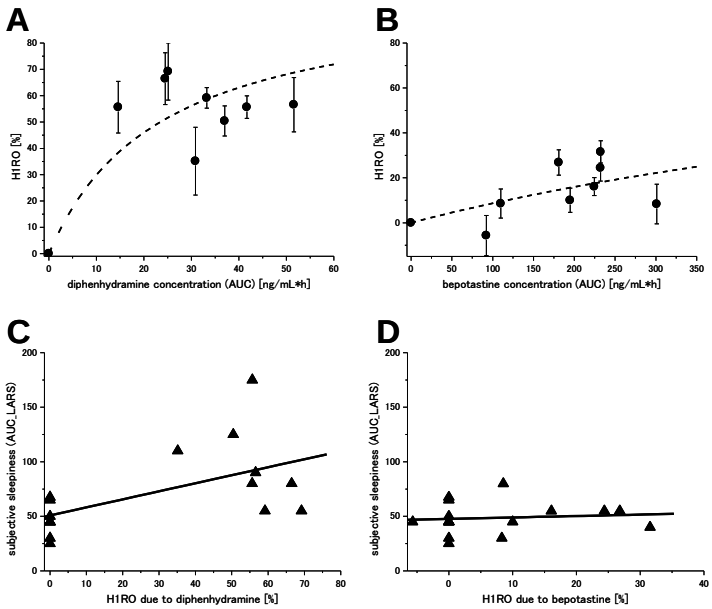


Figure 4. Relationship between mean H_1RO, plasma concentration and subjective sleepiness following administrations of bepotastine and diphenhydramine. Relationship between H_1RO and plasma concentrations was examined for diphenhydramine (A) and bepotastine (B) where the plasma concentrations of these antihistamines are presented as area under the curve (AUC). H_1RO of diphenhydramine rapidly increases with plasma concentration while H_1RO of bepotastine gradually increases with plasma concentration. Error bars represent intra-individual variability (S.D.). Subjective sleepiness (presented as AUC of line-analogue rating scale curve: AUC_LARS) demonstrates mild correlation to mean H_1RO due to diphenhydramine (C), while subjective sleepiness due to bepotastine demonstrates no correlation to mean H_1RO due to bepotastine (D). *Reproduced from the reference [10] by courtesy of Blackwell Publishing Company.