VIII. 3. Brain Histamine H₁ Receptor Occupancy of Antihistamines, Bepotastine and Diphenhydramine, Measured by [¹¹C]Doxepin PET

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Introduction

Histamine H₁ receptor (H₁R) antagonists, or antihistamines, are often used for treatment of allergic disorders such as seasonal rhinitis. Antihistamines mainly act on the peripheral tissues but can induce sedation. This undesirable central side effect is caused by blockade of nerve transmission in the histaminergic neuron system which projects from the tuberomammillary nucleus in the posterior hypothalamus to almost all cortical areas¹⁻³. First-generation antihistamines, such as diphenhydramine and d-chlorpheniramine, that can easily penetrate blood-brain barrier (BBB) tend to occupy a large proportion of post-synaptic H₁Rs⁴⁻⁶. Second-generation antihistamines, such as fexofenadine, cetirizine and olopatadine, can slightly penetrate BBB and H₁Rs are slightly occupied as having been demonstrated using positron emission tomography (PET)⁴⁻⁷⁻⁹. Variation in cerebral H₁R occupancy (H₁RO) of antihistamines results mainly from their different BBB permeability. Thus, sedative property of antihistamines can be evaluated in terms of H₁RO measured with PET and [¹¹C]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 [¹¹C]doxepin in a crossover study-design. Binding potential ratio and H₁R occupancy values were
calculated using placebo data, and were compared between bepotastine and diphenhydramine. PET brain images, after being corrected for tissue attenuation, were reconstructed with a filtered back projection algorithm. The brain images were then normalized by plasma radioactivity at 10 min post-injection to yield static distribution volume (DV) images according to our static scan protocol reported previously. For visualization at a whole-brain level, DV brain images were analyzed statistically on a voxel-by-voxel basis by Statistical Parametric Mapping (SPM2). Differences in parameter values between bepotastine, diphenhydramine and placebo (control) were statistically examined, and regional maxima of statistical significance (p< 0.001) were projected onto the surface-rendered MRI-T1 standard brain images.

Results

Brain images following administration of bepotastine demonstrated slightly lower binding potential in comparison to those following placebo, and images following diphenhydramine administration demonstrated significantly lower binding potential in comparison to both placebo and bepotastine (Figure 1). Using SPM2 on a voxel-by-voxel basis, parametric brain BPR images following treatment with bepotastine or diphenhydramine were statistically compared to those following treatment with placebo. Areas such as ACC, MPFC and DLPFC, TC demonstrated significantly low BPRs after treatment with diphenhydramine as compared to treatment with placebo. On the other hand, SPM analysis did not reveal any brain area where BPRs were significantly lower following treatment with bepotastine than following treatment with placebo. Overall cortical mean H1RO of bepotastine and diphenhydramine were 14.8% and 56.8%, respectively. H1R occupancy of both bepotastine and diphenhydramine correlated well with their respective drug plasma concentration (p< 0.001).

Discussion

Human molecular imaging, especially a non-invasive imaging of biological phenomena at a molecular level in living human brain, has been actively conducted. In the present study, H1RO of bepotastine, a second-generation antihistamine, was compared to that of diphenhydramine, a typical sedative antihistamine, in a single-blinded placebo-controlled crossover study-design. H1RO after a single oral administration of bepotastine 10 mg or diphenhydramine 30 mg was calculated as approximately 14.8% and 56.8%, respectively. It has also been reported that, single-oral administration of
d-chlorpheniramine (2 mg) achieved approximately 50 to 77% of H1Rs. As a whole, previous PET studies demonstrated that first-generation antihistamines occupied more than 50% of available H1Rs.

On the other hand, H1RO after single-oral administration of bepotastine (5 mg) was much lower than that of first-generation antihistamines (15% vs. 50%). This result is in accordance with the categorization of bepotastine as a second-generation antihistamine. Previous studies have demonstrated H1ROs due to other second-generation antihistamines: epinastine 20 mg (8.2 to 13.2%)\(^5,6\), terfenadine 60 mg (12.1-17.1%)\(^4,6\), astemizole 10 mg (28.7%), azelastine 1 mg (20.3%), mequitazine 3 mg (22.2%)\(^6\) and ebastine 10 mg (9.9%)\(^6\). As a whole, second-generation antihistamines would occupy around 0 to 20% of brain H1Rs\(^6\). Later, single-oral doses of cetirizine 20 mg and fexofenadine 120 mg, both double oral doses in Japan, were reported to achieve 26% and 0%, respectively\(^6\). Based on such findings, second-generation antihistamines can be further separated into two subgroups according to their BBB permeability\(^2,3\); a category that cause little sedation at low doses, but cause dose-related cognitive impairment at higher doses as seen with cetirizine, and the other category that does not cross BBB and therefore induces no sedation even at exceeded doses as seen with fexofenadine\(^9\).

The reasons for the small number of placebo-controlled crossover studies would be their disadvantages such as increased radiological exposure to subjects as the same subject is scanned more than twice. Investigators are therefore advised to minimize total radiation exposure to subjects by choosing a minimum radiological dose and by using 3D data acquisition mode with high sensitivity. In addition, mental and physical stress of the subjects should be reduced by simplifying measurement protocol, as in the present study where complete dataset were obtained for all of the eight subjects. In a previous study, only 6 of the 11 subjects completed all of the four 100-min-long PET scans planned, possibly suggesting how hard it is to conduct crossover PET studies\(^11\).

In summary, we examined H1RO of bepotastine at its recommended single oral dose (10 mg) and compared it to that of single oral administration of diphenhydramine (30 mg) using PET measurement in a placebo-controlled crossover study. Bepotastine occupied approximately 15% of available H1Rs in human brain while approximately 57% of H1Rs were occupied by 30 mg of diphenhydramine. It is therefore suggested that oral administration of bepotastine (10 mg), with its low H1RO and thus minimal sedation, could safely be used an anti-allergic treatment for various allergic disorders. It would be of a great benefit to estimate the appropriate therapeutic doses of new antihistamines and other
drugs using PET measurement and the smallest number of volunteers\textsuperscript{6-10).} Collection of more H1RO data is encouraged for establishment of a reliable international database for evaluation of the sedative profile of antihistamines.

References


Figure 1. Mean brain images of healthy volunteers after administration of placebo, bepotastine and diphenhydramine.