VIII. 8. Hangover Effect of Orally Administered Antihistamines Measured by Brain Histamine H_1 Receptor Occupancy Using PET and ^{11}C-doxepin: A Comparison between Diphenhydramine and Bepotastine in Healthy Subjects

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Introduction

Most of us have, at least once, received antihistamine medication for treatment of allergic diseases, common cold, cough, fever, or motion sickness. The most undesirable central nervous system side-effect of antihistamines is sedation[1)], which is considered to be attributed to their penetration across the blood-brain-barrier (BBB) and blockage of the brain histamine H_1 receptors (H_1Rs) which promotes wakefulness and cognition[2)]. To avoid daytime sedation, antihistamines are often administrated at night. However, the residual sedative effect of antihistamines, so-called ″hangover effect″, has poorly been evaluated, although it can negatively affect daily activities as the actual acute effects do. Subjective questionnaires or psychomotor-task-based evaluations of antihistamines-induced hangover effects[3-5)] have so far failed to provide a quantitative index, making it difficult to compare inter-drugs differences obtained from different experiments.

Using positron emission tomography (PET), antihistamines ability to penetrate across the BBB and cause sedation could be evaluated in terms of brain H_1R occupancy (H_1RO)[6)]. In this study, we evaluated the next-day hangover effect of two antihistamines, specifically, diphenhydramine and bepotastine, the first- and second-generation an

Methods

This study was approved by the Committee on Clinical Investigation at Tohoku

University Graduate School of Medicine and was performed according to the criteria of the Declaration of Helsinki. All experiments were performed at the Cyclotron and Radioisotope Centre, Tohoku University. Eight healthy male volunteers (mean age ± SD: 22.6±2.1 yrs old) received a single dose of diphenhydramine 50 mg (DREWELL®), bepotastine 10 mg (TALION®) or a placebo orally at bedtime (11 p.m.) in a double-blinded, crossover manner with minimum washout-time of 7 days. PET measurement was performed at 11 a.m. the next morning (12 hr post-drug). Blood samples were collected for measuring plasma drug concentration and individual subjective sleepiness is measured using Line Analogue Rating Scale (LARS) and Stanford Sleepiness Scale (SSS). PET brain images, after being corrected and reconstructed, was considered to reflect the distribution volume (DV) according to our previous investigation on static scan protocol[7]. PET brain images obtained from each subject were then co-registered using their T1-weighted magnetic resonance images (MRI) using Statistical Parametric Mapping software (SPM2). Regions of interest (ROIs) were defined in the cortical regions and binding potential ratio (BPR) and H_1R occupancy (H_1RO) values were calculated using placebo data, and were compared between bepotastine and diphenhydramine.

For visualization at a whole-brain level, DV brain images were also analyzed statistically on a voxel-by-voxel basis using SPM2. Differences in parameter values between bepotastine, diphenhydramine and placebo were statistically examined, and regional maxima of statistical significance ($P<0.001$) were projected onto the surface-rendered MRI-T1 standard brain images.

Results

^{11}C-Doxepin radioactivity distribution patterns were similar in the subjects treated with bepotastine or placebo. However, in the subject treated with diphenhydramine, ^{11}C-doxepin radioactivity distribution appeared much lower than that in bepotastine or placebo, reflecting a much lower specific binding density at 12 hr post-dosing with diphenhydramine. Parametric brain BPR images following treatment with diphenhydramine or bepotastine were statistically compared with those obtained following treatment with the placebo. Brain regions with statistically lower BPRs ($P<0.001$) are found in most brain regions, including ACG, PFC, TC and OC, on the other hand, the difference in BPRs between the subjects treated with bepotastine and those treated with the placebo was negligible. Calculation of BPR in the different ROIs revealed significantly

lower values in the case of diphenhydramine than in the case of bepotastine or the placebo (P<0.05) in all cortical regions studied, although no significant difference between bepotastine and the placebo was observed. Overall cortical mean H_1RO of bepotastine and diphenhydramine were 16.6% and 44.7%, respectively. H_1RO of both antihistamines are not correlated with their respective subjective sleepiness.

Discussions

Though the hangover effect of antihistamines has been noticed almost simultaneously as their acute sedative effect as established in some early papers showing that promethadine, diphenhydramine, and chlorpheniramine, induce after-morning drowsiness after single or repeated administration[3, 8], the Objective assessments are rare. Alford C. *et al*. reported that the hangover effect of hydroxyzine (50 mg) can be detected by continuous electroencephalography (C-EEG), which reveals increased total drowsiness scores[4]. Boyle J. *et al*. clearly differentiated the hangover effect of first- and second-generation products, specifically, chlorpheniramine and fexofenadine, using polysomnography and performance tasks in a normal-volunteers-involved, placebo-controlled study[5]. However, these assessments have so far failed to provide a quantitative index which can compare inter-drugs differences obtained from different experiments. In this study, the hangover effect of diphenhydramine and bepotastine are quantitatively evaluated in terms of H_1RO at 12 hr post-dose (45% and 17%, respectively). Since we have previously confirmed that H_1RO at Tmax of non-sedating antihistamines is less than 20%[9]. Once H_1RO reaches 50%, sedation is almost inevitable, as seen in many original products[10-12]. These results are agree with the results of proportional impairment ratios (PIRs)[1] and psychomotor study. In this study, the relatively high H_1RO of diphenhydramine, i.e. 45% at 12 hr post-dose suggests a predominant residual sedative effect and therefore increased possibility of sedation. On the other hand, the low H_1RO of bepotastine (less than 20%) supports its non-sedative effect at standard oral dose (10 mg), suggesting that second-generation antihistamine, being free of hangover, may be superior to the classical antihistamines in treating allergic diseases.

In contrast to the highly sensitive PET measurement, it is widely accepted that subjective sleepiness is not a reliable mean for assessing the sedative effect of antihistamines because this parameter is affected by many internal and environmental factors. It is thus not surprising in this study that no inter-drug difference in subjective

sleepiness at 12 hr post-dose was observed. To that end, impairment of objective performance has in some cases been established in the absence of subjective sleepiness following treatment with antihistamines[13,14]. Therefore, those who believe that lack of sleepiness means a better response are probably mistaken and are prone to have a higher sedation-related detrimental risk than those who feel sleepy. The lack of correlation between H_1RO and sleepiness scores in this study further suggests that assessment of antihistamines hangover effect should not be made based on subjective feelings alone.

In summary, we have demonstrated that nighttime-administrated diphenhydramine results in a hangover effect, whereas the non-sedative bepotastine is hangover free the next day. To the authors' knowledge, this is the first study evaluating the residual sedative effect of antihistamines using PET. It must be emphasized that sedating OTC-antihistamines, including diphenhydramine, are often self-administrated by active, healthy individuals during their important years of middle life. The clinical benefits of this treatment need to be weighed carefully against the risks, taking into account drug hangover effect. Further work is encouraged to reaffirm the findings of the present study in repeated dose studies or in patients with chronic allergic conditions.

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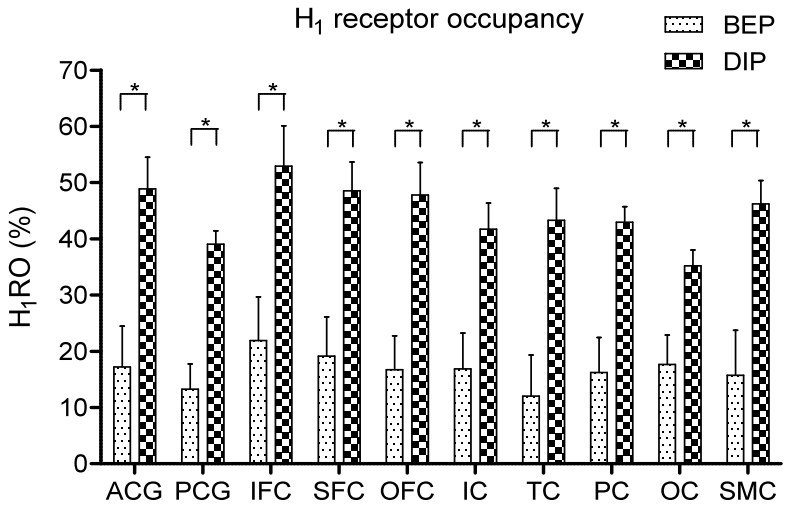

Figure 1. Region of interest (ROI) -based analyses of histamine H_1 receptor occupancy (H_1RO) in the cortex region. *P<0.01, paired-t test. Error bars represent inter-individual variability (S.E.M.). ACG and PCG, anterior and posterior cingulate gyri, respectively; PFC, prefrontal cortex; OFC, orbitofrontal cortex; IC, insular cortex; TC, temporal cortex; PC, parietal cortex; OC, occipital cortex; SMC, sensorimotor cortex.