

## Sedative Profiles of Second-generation Antihistamines

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### Introduction

Effective and safe treatments are required to relieve symptoms and improve the health-related quality of life of the millions of individuals who suffer from allergic symptoms<sup>1)</sup>. Oral antihistamines represent a mainstay of treatment because of their potent inhibition of the allergic response. However, many antihistamines are associated with central nervous system (CNS) effects because of their lack of exclusive selectivity for the H<sub>1</sub>-receptor and their capacity to penetrate the blood-brain barrier (BBB)<sup>2)</sup>. Sedation and psychomotor impairment associated with antihistamines can have serious safety implications. The performance of everyday activities, such as car driving, in addition to tasks that require high levels of concentration, can be impaired after the administration of some antihistamines, with subsequent potentially serious, even fatal, consequences<sup>3)</sup>. It is accepted that older-generation antihistamines have sedative and impairing effects at recommended doses, which prompted the development of newer agents devoid of such effects. However, newer-generation antihistamines are associated with divergent sedative profiles, so there remains a need to establish reliable and sensitive tests to evaluate this property<sup>2)</sup>.

This study was once reported as a work in progress and this time the complete results are reported here. This study employed a variety of tests to examine their relative sensitivity and to establish the sedative profiles of three antihistamines – hydroxyzine (HYD; verum control), cetirizine (CET) and fexofenadine (FEX) – compared with placebo. Written informed consent was obtained from all study participants. Study subjects were assessed in terms of: How sleepy they felt and how their performance was objectively

impaired using a series of laboratory tests (Study 1). How their performance was impaired in a 'real-life' scenario, using a car driving test (Study 2). The extent to which antihistamines bound to cerebral H<sub>1</sub> - receptors using positron emission tomography (PET) (Study 3). Studies 1 and 2 were conducted at CYRIC, Tohoku University.

### **Materials and Methods**

Study 1: A total of 20 healthy adults males (mean age  $23.1 \pm 2.8$  years) were recruited into this double-blind, placebo- and verum-controlled study. Subjects were randomized to receive FEX 120 mg, CET 20 mg, HYD 30 mg and placebo in a crossover fashion. Subjective sleepiness was assessed using the Stanford Sleepiness Scale (SSS). This test was performed before and at 90 minutes after study drugs were administered, at which point visual cognitive function tests were also performed. The visual cognitive function tests were analyzed using two variables: (1) reaction time (RT) and (2) correct answer rate (AR). Both RT and AR were obtained for each subject who each performed a series of six tests.

In the first test (choice reaction time: CRT), subjects were presented with an image to the left or right of a screen and were asked to respond by pressing the left-hand button if the image was on the right, and vice versa. Similar to the CRT, the simple reaction time test (SRT) involved the random presentation of images on the screen, to which the subject was asked respond by pressing the right-hand button as quickly as possible. The third test, comprising four different subtests, was a visual discrimination task (VDT). A total of 120 images were presented with different exposure durations such as 3, 5, 7 or 20 msec and subjects were asked to respond only when figures, not letters were presented.

Study 2: A total of 18 healthy adults males (mean age  $23.4 \pm 1.6$  years) were recruited into this double-blind, placebo- and verum-controlled crossover study. Each subject was administered FEX 120 mg, HYD 30 mg (verum control) and placebo and asked to perform a series of car braking tests using a system provided by Prof. Hindmarch (Human Psychopharmacology Research Unit, Surrey Univ., UK) with agreement of his group. Subjects were asked to press a brake pedal when a light on the bonnet was lit, a process which occurred 25 times at random intervals during each test. The brake reaction time (BRT) and subjective sleepiness were measured for each individual during each test. Tests were performed before and at 90 and 240 minutes after administration. During each test, subjects inserted an earphone to enable them to talk on a mobile phone. The four test

driving conditions for BRT were when:

- 1) Not talking on mobile phone while driving,
- 2) Driving and answering simple arithmetic questions on the mobile phone,
- 3) Driving and answering complex arithmetic questions on the mobile phone,
- 4) Driving and answering questions on a specific theme (such as a favorite movie).

Study 3: Eleven healthy males (mean age  $23.1 \pm 2.8$  years) underwent brain positron emission tomography (PET) after randomization to receive either FEX 120 mg or CET 20 mg. Dynamic scanning of each subject was performed for 90 minutes, starting at 90 minutes after drug administration (corresponding to the  $T_{max}$  of the agents), at which point subjects were also administered intravenous  $^{11}\text{C}$ -doxepin, a selective radioligand for the  $\text{H}_1$ -receptor. To calculate the  $\text{H}_1$ -receptor occupancy ( $\text{H}_1\text{RO}$ ) of each drug, the binding potential ( $\text{BP}$ ;  $\text{Bmax}/\text{KD}$ ) of each agent in each region of interest (ROI) in the brain was calculated, as described elsewhere<sup>4,5</sup>. BP images were created, from which  $\text{H}_1\text{RO}$  was calculated for the frontal cortex, anterior cingulate gyrus, temporal cortex, parietal cortex and occipital cortex, using the mean BP values of placebo condition obtained in other additional subjects. The  $\text{H}_1\text{RO}$ s of FEX and CET were calculated using the following equation:

$$\text{H}_1\text{RO} = [(\text{mean BP of control} - \text{mean BP with each drug})/\text{mean BP of control}] \times 100.$$

## Results

Study 1: As for the change in mean RT before and after medication (Figure 1), in five of six cognitive tasks, HYD was significantly more impairing than placebo. FEX did not differ significantly from placebo in terms of impairment. CET was significantly more impairing than FEX in CRT test ( $p=0.008$ ). The results of AR showed similar tendency. As for subjective sleepiness, FEX resulted in indistinguishable sleepiness compared with placebo. Trends towards increased sleepiness with HYD and CET compared with placebo and FEX were observed, although these did not reach statistical significance. In addition, increased sedation was reported with CET compared with FEX in one task.

Study 2: Significant sedation was observed with HYD at 90 and 240 minutes after administration, as assessed by the SSS ( $p=0.017$  and  $p=0.003$  versus placebo, respectively). No significant subjective sedation was observed with FEX compared with placebo (Figure 2) ( $p>0.05$ ). At 240 minutes, HYD significantly prolonged BRT compared with

placebo under all test conditions except when driving but not talking on the mobile phone ( $p<0.05$ ). At 240 minutes, HYD prolonged BRT significantly compared with FEX when driving and performing simple arithmetic, and when driving and talking on a mobile phone ( $p<0.05$ ). Interestingly, prolongation in BRT seems more influenced by a dual task situation caused by cellular phone talks during driving than an administration of HYD, a sedative drug (Figure 2).

Study 3: Sample PET scans of an individual subject are shown (Figure 3). The brighter the region, the greater the concentration of free  $H_1$ -receptors to which  $^{11}C$ -doxepin molecules bind, or the lower the concentration of antihistamine penetrating BBB. CET binds more readily to cerebral  $H_1$ -receptors than either FEX or placebo, as evidenced both from the PET images and the  $H_1RO$  calculations. CET was observed to occupy  $H_1$ -receptors in the cerebral cortex (20 to 30%). In contrast, FEX occupied receptors in the cerebral cortex to lesser extent (0 to 5.6%).

## Discussion

The twin purposes of performing and comparing the three different studies were to evaluate the relative sensitivities of each test to detect impairment by antihistamines and to explore the impairment profiles of FEX, CET and HYD. The results of Study 1 demonstrate that evaluation of subjective sleepiness using the SSS sometimes cannot distinguish clearly between the known sedative effects of the positive control, HYD, and placebo. Although the results of the SSS suggest a trend in increasing sleepiness: FEX=placebo < CET < HYD, these differences were not statistically significant. However, this relationship was confirmed by the results of the objective psychomotor tests performed in the laboratory in Study 1. Then, it seems that objective psychomotor tests are more sensitive than measurement of subjective sleepiness.

Study 2 was conducted to determine if the results of an objective ‘real-life’ test of impairment could “mirror” the results obtained in the laboratory and to assess patients’ reactions to performing dual tasks of varying difficulty. An additive impairing effect was observed when subjects performed dual tasks simultaneously following administration of HYD, which was not observed after administration of FEX. Since the dorsolateral prefrontal cortex, which is postulated to be involved when performing the multiple tasks demanded of the driving study (Study 2) simultaneously, is relatively abundant in histamine  $H_1$ -receptors, this brain region is likely to be affected strongly by antihistamines that can penetrate the BBB<sup>6</sup>. The results suggest that an experiment in real-life situation is less

sensitive than that done in laboratory situation.

The results of Studies 1 and 2 imply that HYD crosses the BBB, binds to receptors in the cerebral cortex, thus resulting in impairment, whereas FEX does not. Study 3 confirmed that FEX does not penetrate the BBB, in contrast to CET, which had an H<sub>1</sub>RO rate of around 20 to 30% depending on the ROI. The PET results suggest that the impairing properties of CET demonstrated in some psychomotor tests in Study 1 could be attributed to the binding of the antihistamine to cerebral H<sub>1</sub>-receptors.

## Conclusions

These studies suggest that sensitivities of the methods are as follows: [BRT study in real-life situation]= [subjective sleepiness]< [psychomotor study in a laboratory]< [H<sub>1</sub>RO measurement with PET]. These studies also suggest that antihistamines increase in their impairing potential in the following order: FEX< CET< HYD. Further, FEX has a similar sedative profile to placebo. A multidimensional testing system is required to establish the relative impairment profiles of antihistamines, since a single test cannot reveal H<sub>1</sub>RO, how sedated patients feel and how well they perform a diverse range of tasks. Further testing is required of all newer-generation agents to confirm their relative propensity to cross the BBB and cause impairment.

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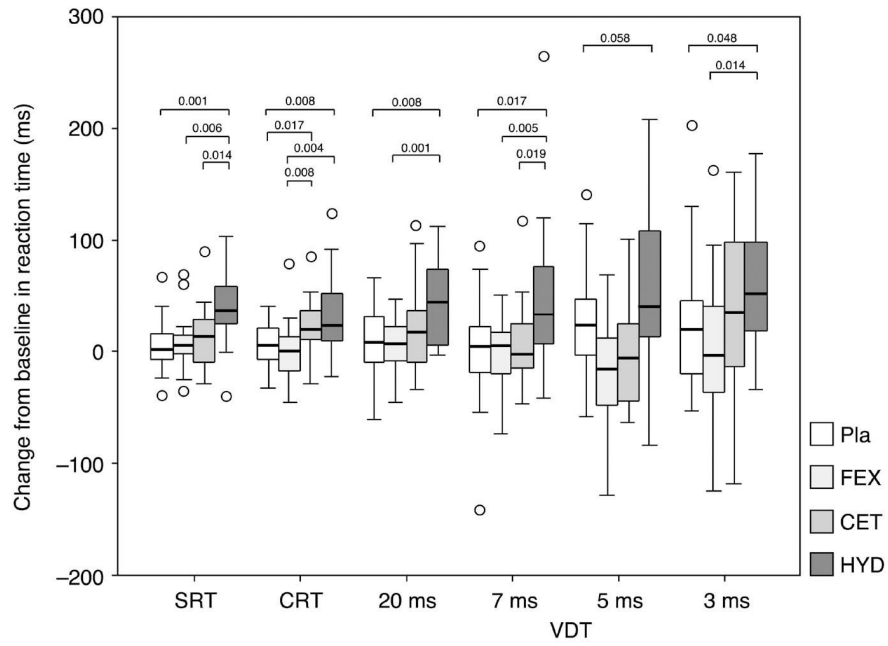


Figure 1. Change in the mean reaction time before and after medication. Statistical examination was done by Friedman's test followed by post-hoc Bonferroni test (ref.7).

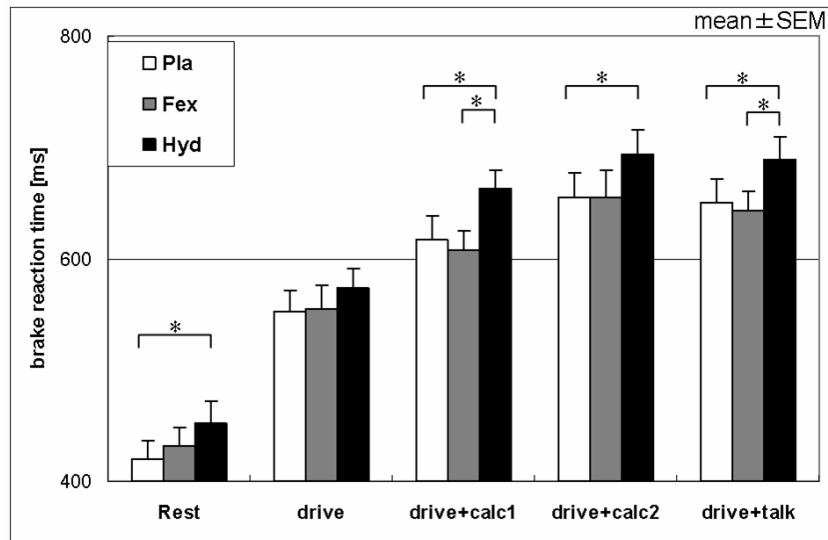


Figure 2. Results of BRT measurement in car driving study. \* statistically significant examined by Friedman's test followed by post-hoc Bonferroni test ( $p < 0.05$ ).

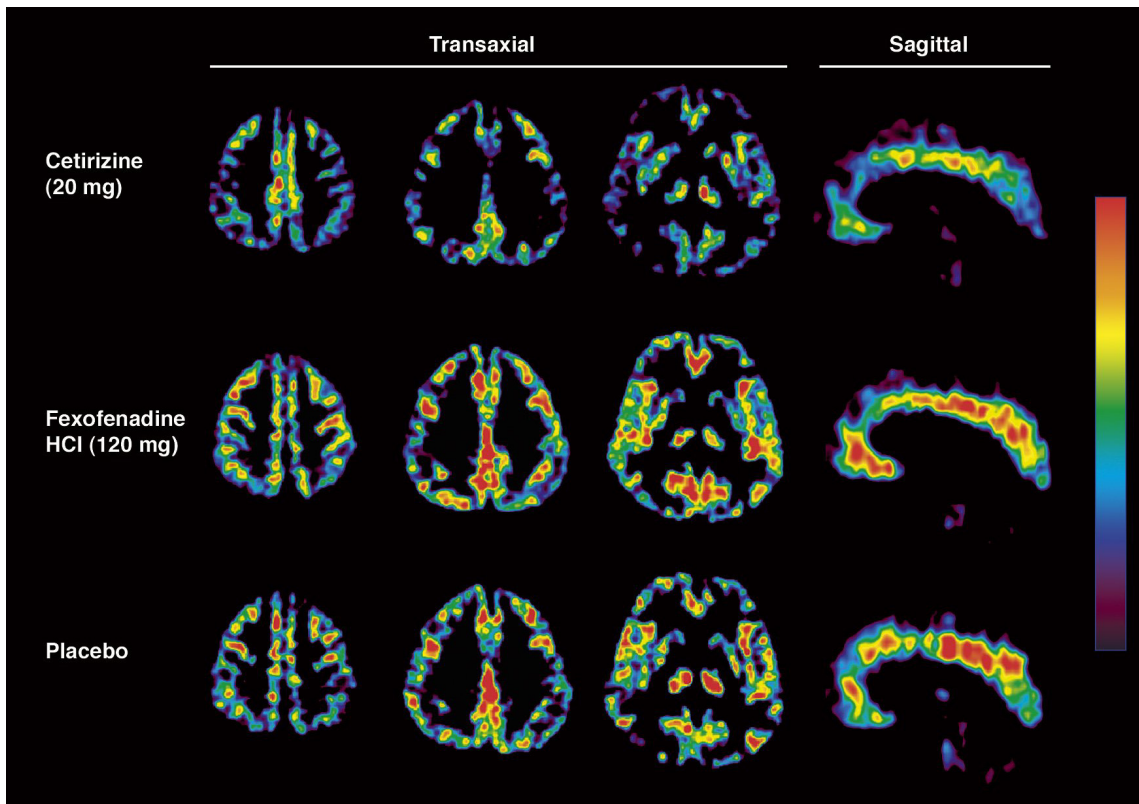


Figure 3. PET scans of brain regions after administration of CET, FEX and placebo. Images after administration of CET show lower binding of <sup>11</sup>C-doxepin compared to other conditions (FEX and placebo) (ref.7).