ABSTRACT

Although second-generation antihistamines generally penetrate the blood-brain barrier to a lesser degree than the powerfully impairing first-generation antihistamines, many have been found to produce dose-related impairment of central nervous system (CNS) function. In contrast, fexofenadine has been determined to be truly nonimpairing, even at supraclinical doses. Crossover studies using placebo- and positive-controlled objective tests of impairment showed that choice reaction time, sensorimotor coordination, information processing, car driving skills, and electrophysiologic measures were unaffected in patients taking fexofenadine. In addition, recent positron-emission tomography studies have provided further evidence that fexofenadine does not penetrate the blood-brain barrier. Therefore, in terms of CNS function, fexofenadine can be differentiated from the other currently available antihistamines.


THE PSYCHOPHARMACOLOGY OF ANTIHISTAMINES: INDICES OF BEHAVIORAL TOXICITY*

Ian Hindmarch, PhD

ABSTRACT

A ny central nervous system (CNS) side effects caused by pharmacologic therapy can have important safety and quality-of-life implications. Histamine has been widely reported to play an important role in maintaining CNS arousal and alertness. Therefore, antihistamines that cross the blood-brain barrier and antagonize histamine-1 (H1)-receptors in the brain can produce impairment of cognitive functions, including attention, memory, sensorimotor coordination, information processing, and psychomotor performance. These are related to the information-processing demands of all human day-to-day activities and functions, and therefore, administration of agents that cross the blood-brain barrier and impair CNS functions may lead to serious issues of patient safety as well as affect the quality of life of patients. For example, CNS impairment will not only impair the ability to drive and operate machinery, but will affect activities such as classroom learning, causing patients to feel tired, sleepy, and unable to concentrate.

Evidence from epidemiologic studies has begun to determine a relationship between an increased incidence of automobile accidents and the administration of antihistaminergic agents; 3% of patients involved in fatal road traffic accidents (RTA) were found to have previously taken an antihistamine. Furthermore, 72% of patients who have used an antihistamine and subsequently been involved in a fatal RTA have been determined to be culpable, compared with 86% of those who had consumed alcohol. It has also been suggested that, cerebral H1-blockade is associated with falls in the elderly.

OBJECTIVE MEASUREMENTS OF CNS IMPAIRMENT

Assessment of the CNS effects produced by various
drugs, such as antidepressants, hypnotics, and anxiolytics, using objective psychometrics has been a common practice within psychopharmacology since the late 1960s.10 However, the rigorous testing of antihistamines to ensure the CNS safety of these agents is a relatively more recent development.11 In order to evaluate impairment properly, there is a need for objective assessments and pharmacologic evidence that is not solely reliant on a patient's subjective perception of tiredness and sleepiness. Penetration into the CNS can be measured objectively using psychometric tests, developed specifically to assess the central effects of drugs, and also by positron-emission tomography (PET) imaging. It is important that objective assessments include placebo and positive (verum) controls. Placebo is used to control the measured effects of the experimental drug treatment and the verum to validate the sensitivity of the psychometric assessments.

There are numerous psychometric assessments, but among the most frequently used are critical flicker fusion threshold (CFF), choice reaction time (CRT), continuous tracking task (CTT), and brake reaction test (BRT).12 The CFF assesses CNS arousal and information-processing capacity, which is the ability to discriminate discrete bits of sensory information. The amount of information the brain can process with respect to time is measured by discriminating flicker from fusion and vice versa in a set of light-emitting diodes.3 This test has been shown to be sensitive to a number of psychoactive compounds including antidepressants, anxiolytics, caffeine, hypnotics, neurotropics, antihistamines, and phytopharmaceutical agents.13,14 Choice reaction time is used to measure drug-induced changes in psychomotor speed. There are 3 main components of reaction time: total reaction time (TRT) from stimulus onset to completion of response; motor reaction time (MRT), which measures the time to move the finger between the start and the response buttons; and the processing or recognition reaction time (RRT), which is obtained from subtracting MRT from TRT.3 The compensatory tracking task is a sensitive and reliable interactive task of sensorimotor function and involves tracking a moving arrow on a visual display unit. The test also includes a divided attention measure of peripheral reaction time.3

In addition to laboratory objective tests, real-life situations can be simulated using on-the-road car driving. For example, BRT is a measure of some of the cognitive and psychomotor functions involved in car driving, including attentional efficacy. The aim of the test is to measure the time taken for a subject to turn off a red brake light mounted on the hood of the car by depressing the brake pedal. The light, which is illuminated randomly during the test, simulates the rear brake light of an imaginary car in front of the test car.

PET imaging using [11C]-doxepin, a radioactive tracer, is a reliable method for investigating the distribution of cerebral H1-receptors and the blocking effect of antihistamines.4 When [11C]-doxepin is bound to H1-receptors, its presence can be detected by monitoring the photons that it emits. This emission can be visualized on PET scans by using different grey scales or colors to indicate different levels of binding. Receptor blockade by another substrate, such as an antihistamine, blocks the binding of the tracer and subsequent photon emission; only background emission from H1-receptor-poor regions, vascular regions, and areas of nonspecific binding can be seen.

**Behavioral Toxicity Indices**

In order to compare the CNS effects of different antihistamines, the impairment/nonimpairment (I/NI) ratio for behavioral toxicity can be used. This is determined as the ratio of the number of psychometric assessments demonstrating significant impairment compared with the number of psychometric assessments showing no impairment. Testing at supraclinical doses is particularly important in determining behavioral toxicity as many patients have a clinical need for high therapeutic doses, particularly in the management of urticaria and other dermatologic conditions. Patients also self-dose to concentrations above those recommended by the manufacturers, and many take concomitant medications, which may result in increases in antihistamine plasma concentrations due to drug-drug interactions.15 In addition, any impairment occurring at supraclinical doses indicates that the antihistamine in question is able to cross the blood-brain barrier and will do so whatever the dose administered, leading to a potential impairment of CNS functions even at standard recommended doses.

Three types of antihistamines have been identified by behavioral toxicity indices. First-generation antihistamines (eg, promethazine, diphenhydramine, and chlorpheniramine), although efficacious, pass freely across the blood-brain barrier and can access cerebral H1-receptors, causing powerful impairment of CNS
functions at clinical and supraclinical doses. In addition, many second-generation antihistamines, such as loratadine, desloratadine, and cetirizine, also penetrate the blood-brain barrier and produce CNS impairment, although to a lesser degree than first-generation drugs. The impairment with second-generation antihistamines is dose related, and care must be exercised with doses in excess of manufacturers' recommendations. In contrast, third-generation antihistamines, such as fexofenadine, can be defined as those that do not penetrate the blood-brain barrier even following a dose-escalation challenge and, therefore, do not produce CNS side effects.

The difference between antihistamines in terms of their I/NI ratios has been determined in a meta-analysis of the published data on this group of compounds. Second-generation antihistamines, such as loratadine, cetirizine, and mizolastine, were associated with objectively determined impairment in a number of tests, often at higher doses. In contrast, fexofenadine HCl (at doses up to 360 mg) was not associated with any impairment and therefore has a risk:benefit ratio of zero. The ratios obtained from the objective tests are summarized in Table 1, for some compounds.

The proportional impairment ratio (PIR) is a refinement of the I/NI method for comparing the CNS effects of different antihistamines. A review of interdrug differences using PIRs identified 76 studies of antihistamines in which assessment of impairment was the primary objective. This review again identified fexofenadine as being devoid of impairment. The overall index of behavioral toxicity for some currently available antihistamines as determined by PIR is shown in Table 2.

**High-Dose Clinical Studies**

Fexofenadine has been shown to have no effect on psychomotor and cognitive function at a supraclinical dose of 360 mg. In this recent study, 15 healthy volunteers received fexofenadine 360 mg, promethazine 30 mg (verum control), and placebo in a 3-way crossover, double-blind study. Subjects performed a series of objective cognitive function and psychomotor performance tests including CFF, CRT, and CTT. Fexofenadine was no different from

| Table 1. I/N I Ratios for Diphenhydramine, Fexofenadine, Cetirizine, and Loratadine |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| **Dose (mg)** | **Number of objective tests showing no impairment** | **Number of objective tests showing impairment** | **I/NI** | **Dose (mg)** | **Number of objective tests showing no impairment** | **Number of objective tests showing impairment** | **I/NI** |
| Diphenhydramine | 25 | 5 | | 50 | 23 | | 100 | 3 | | 150 | 5 | |
| Loratadine | 10 | 16 | 3 | 0.36 | 20 | 8 | 2 | | 40 | 4 | 5 | |
| Cetirizine | 2.5 | 3 | 1 | 0.17 | 5 | 11 | 1 | | 10 | 24 | 3 | | 15 | 1 | 2 | |
| 20 | 9 | 2 | | Fexofenadine | 80 | 3 | 0.00 | | 120 | 9 | | | 180 | 7 | | | 240 | 6 | | | 360 | 6 | |

I/NI = impairment/nonimpairement ratio.

| Table 2. Proportional Impairment Ratios (PIRs) of Some Antihistamines |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| **Antihistamine** | **Dose (mg)** | **PIR** | **Antihistamine** | **Dose (mg)** | **PIR** | **Antihistamine** | **Dose (mg)** | **PIR** |
| Fexofenadine | 80–360 | 0.00 | Cetirizine | 2.5–20 | 0.18 | Loratadine | 10–40 | 0.58 |
| Diphenhydramine | 25–150 | 2.05 | Promethazine | 10–50 | 3.14 | | | | |

placebo in any of the tests, while promethazine significantly impaired subjects in all assessments, thus demonstrating the validity of this approach. The effects of placebo, fexofenadine, and promethazine on CFF thresholds are shown in Figure 1. Therefore, fexofenadine has been identified as being devoid of CNS effects even at supraclinical doses and can be classified separately from other currently available antihistamines. These results support the findings from other clinical studies that have shown no sedation or impairment with fexofenadine.

The lack of sedation or impairment observed with fexofenadine in clinical studies has recently been supported by pharmacologic evidence. Both qualitative and quantitative cerebral H1-binding data from PET studies show that fexofenadine does not bind to the H1-receptor in the brain, suggesting that it does not cross the blood-brain barrier.

In contrast, preliminary studies employing objective tests of impairment have indicated that the active metabolite of loratadine, desloratadine, causes impairment at doses higher than those recommended by the manufacturer. At 20 mg, desloratadine significantly impaired subjects compared with placebo in a CFF test, as indicated by area under the curve. The positive control promethazine (20 mg) also produced significant impairment compared with placebo, validating the sensitivity of the study. These results support the findings from a dose-ranging study showing that desloratadine is associated with increased somnolence compared with placebo at 10 mg and 20 mg.

Japanese Studies
A recent study undertaken in Japanese volunteers (n=24) has shown that fexofenadine is an intrinsically nonimpairing antihistamine, with no impairment of cognitive and psychomotor performance observed in this population, consistent with findings in Western populations. In this randomized, 4-way crossover, double-blind study comparing the effect of fexofenadine HCl 60 mg and 120 mg and promethazine 25 mg (verum control) with placebo on CFF, CRT, and CTT measurements, promethazine caused significant impairment compared with baseline at 66 test points, including CFF threshold, RRT, tracking accuracy, reaction times to peripheral stimuli, and reaction times in the rapid visual information-processing task test. In contrast, fexofenadine was not significantly different from placebo in any test at any time point.

Pharmacologic Studies
The lack of sedation or impairment observed with fexofenadine in clinical studies has recently been supported by pharmacologic evidence. The central H1-receptor occupancy of different antihistamines has been correlated using PET scanning with 11C-doxepin (a radiolabeled drug that binds to histamine receptors). In one study, PET scans were performed on the same subject at baseline and after administration of fexofenadine, cetirizine, and the first-generation antihistamine diphenhydramine.

The cortical brain areas on the PET scans demonstrated less activity after diphenhydramine 50 mg compared with baseline scans, which indicates cerebral H1-receptor blockade. Cetirizine 20 mg also demonstrated H1-receptor blockade in the frontal cortex. In contrast, cortical brain regions did not show less activity compared with baseline scans even after high doses of...
fexofenadine HCl (360 mg), indicating that fexofenadine did not cause any significant H$_1$-receptor blockade.

**DISCUSSION**

Although second-generation antihistamines are associated with less sedation and impairment than their predecessors, a number of these agents are still associated with impairment at high doses. This is important in terms of patients who self-dose to high concentrations.

Numerous well-performed, objective, sensitive measures of psychomotor and cognitive performance have shown that fexofenadine is truly nonimpairing even at supraclinical doses of up to 360 mg. Studies have also indicated that fexofenadine can be used in aviators and aircrew. Furthermore, PET studies have supported these findings, showing that fexofenadine does not bind to the H$_1$-receptor in the brain, suggesting that it does not cross the blood-brain barrier. Therefore, fexofenadine is safe for use in skilled activities such as driving and machine operation and does not affect day-to-day activities, representing a positive advance in the treatment of a number of allergic diseases, including allergic rhinitis and chronic idiopathic urticaria. In terms of CNS safety, fexofenadine can be differentiated from the other currently available antihistamines.

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