

Specific review of the psychometric effects of cetirizine

Volkerts ER, van Laar M. Specific review of the psychometric effects of cetirizine.
Allergy 1995; 50: 55-60. © Munksgaard 1995.

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Antihistamines are widely prescribed for the treatment of various allergic symptoms. One of the major problems with the older medications is their ability to cross the blood-brain barrier and thus cause sedation, while the newer antihistamines have an improved balance between central nervous system (CNS) and peripheral effects. However, various placebo-controlled studies of the new antihistamines have reported some adverse effects, including fatigue with or without sedation.

In such studies, we must define terms such as "fatigue", "somnolence", or "sedation" exactly. Sedation can be measured objectively and may be defined as impairment of cognitive function and psychomotor performance as determined by tasks such as reaction time (RT). Drowsiness refers to the mental state of subject in terms of an increase in the likelihood of falling asleep. It is usually assessed by using visual analog scales (VAS). Subjects indicate their state on a scale which reads from "I feel wide awake" on the left to "I feel extremely sleepy" on the right. The main problem with subjective assessments is that they can result in bias, and this can often be unconsciously encouraged by the physician conducting the trial. Sleepiness refers to the same mental state as drowsiness. It can be subjectively measured by VAS or objectively measured by electrophysiologic methods, e.g., the electroencephalogram (EEG). If histamine is considered to be a neuromediator involved in the maintenance of vigilance in the CNS, then any H₁-antagonist capable of crossing the blood-brain barrier will induce a significant sedating effect (1). The tendency of antihistamines to cause sedation may be further complicated by the fact that these drugs may induce both subjective feelings of drowsiness and objective levels of cognitive and psychomotor impairment. Patients may be unable to discern the latter two changes, and this is a cause for concern if they must function normally during the day.

Various methods may be used in studies which assess the effects of medications, including antihis-

tamines, on CNS activity. A well-designed study usually includes features such as double blinding with placebo control and use of the therapeutic dosage of the drug under investigation with an active positive control; in an antihistamine study, the latter would be one of the older medications known to cause sedation. It is also important to include a sufficient number of subjects, and all assessments should be made in an appropriate environment and at a relevant time after drug administration. An important additional factor is ascertaining that subjects have been trained to achieve base-line performance standards (see below).

Useful objective measurement of the CNS effects of an antihistamine involves assessing the effects of the drug both on car driving (2, 3) and on psychometric tests in normal volunteers. Since the subjects have to become familiar with the tasks and procedures, they have to attain stable base-line performance levels before administration of any treatment. Subjects who undergo such initial training in psychometric tests usually reach a plateau in their learning curve after about five sessions (Fig. 1). Over the years, the on-road driving test has been applied in studies of the effects of hypnotics, antidepressants, and anxiolytics, and it has

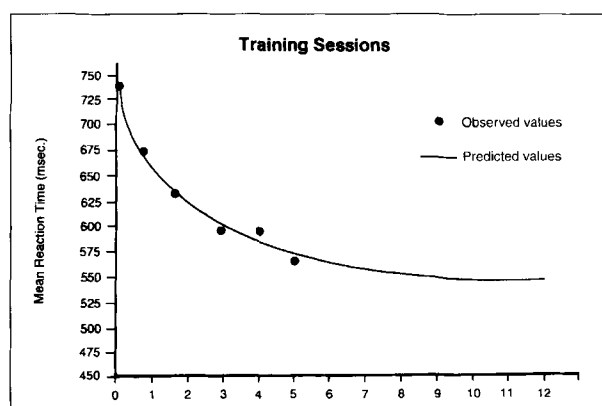


Fig. 1. Learning curve: mean observed and predicted reaction times of 27 subjects in five successive training sessions.

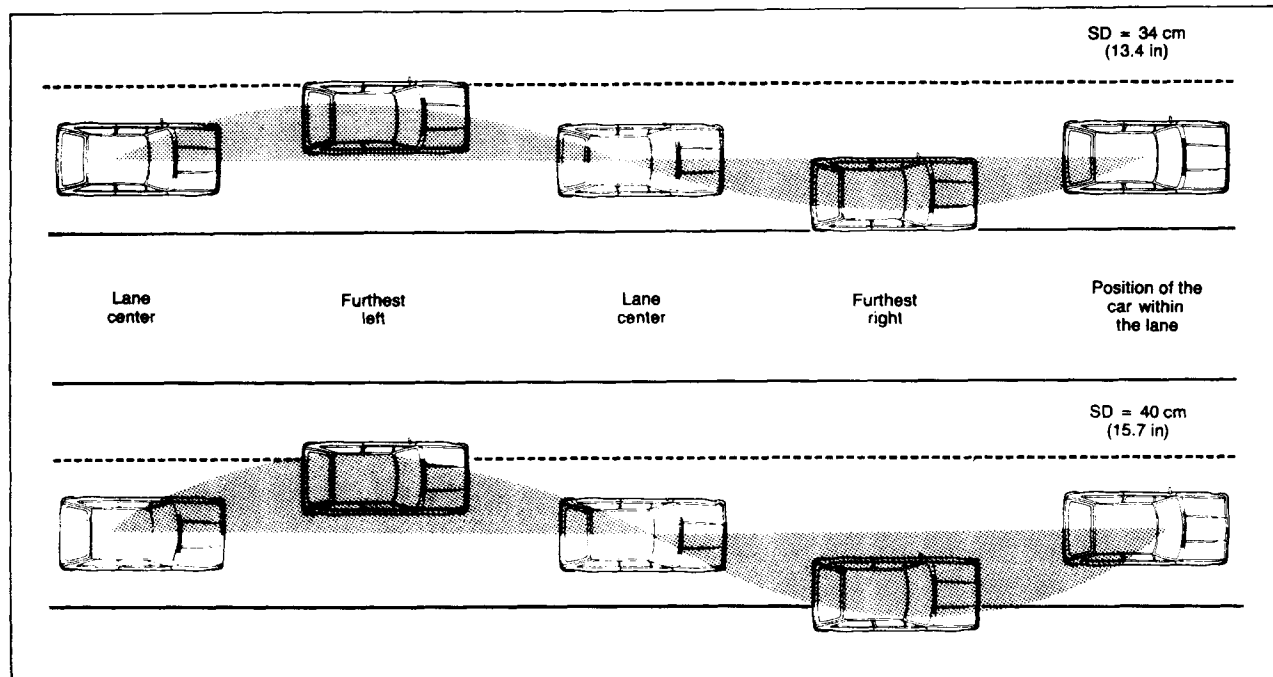


Fig. 2. Illustration of SDLP (standard deviation of lane position).

been shown to be sensitive to drug-induced impairment.

A major advantage of this test is its realistic nature, an aspect which is difficult to simulate in the laboratory. However, the on-road driving test can never fully replace laboratory-based tests; therefore, it is prudent to include other tests such as reaction-time tasks. The car used in the on-road task is specially equipped with an electro-optical lane tracker mounted on the roof and also with dual controls. The former device measures the vehicle's position relative to the lane markings on the road. The subject must keep the car straight without wandering within or outside the lane; thus, the performance of the driver is monitored in a very controlled and reproducible manner. Any deviation in relation to the white line can be measured and is expressed as the standard deviation of lateral position (SDLP). This primary performance measure of the driving test is the amplitude of weaving or side-to-side motion of the car, and it basically indicates the driver's ability to keep the vehicle safely within the lane while traveling on a highway during normal traffic.

The meaning of SDLP is illustrated in Fig. 2. If we assume that the lateral position is distributed normally (Gaussian), as indicated statistically by skew and kurtosis (both having values of about zero), nearly all variability would be contained within a range of 6 cm SD (plus a vehicle width of 1.6 m). A schematic representation of the driving test is given in Fig. 3. If the car is kept absolutely straight, SDLP is zero. In practice, as determined

in placebo conditions of successive investigations over more than 10 years, an SDLP of 18–22 cm is considered to be normal. When $SD=34$ cm (upper part of Fig. 2), the full lateral range would be about 3.6 m, i.e., the width of the lane, indicating that the driver is not in full control of the vehicle. Moreover, unsafe driving becomes more apparent with an SD increment of 6 cm (lower part of Fig. 2; total $SD=40$ cm), indicating that the subject repeatedly drives into the adjacent traffic lane or onto the shoulder, the direction being dependent on the mean lateral position.

By this method, cetirizine (10 mg once daily) was compared with terfenadine (60 mg twice daily and 120 mg once daily) and with the older antihistamine triprolidine (5 mg twice daily) used as a

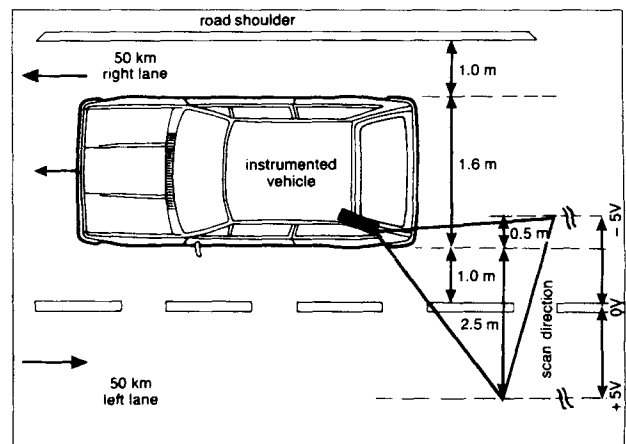


Fig. 3. Schematic representation of on-road driving test.

positive control. All the drugs' effects were tested against placebo. Twenty-seven healthy male volunteers received medication for 4 consecutive days with testing on treatment days 1 and 4. Testing comprised driving a vehicle equipped as outlined above to measure SDLP over a total of 100 km with a total time spent on the task of around 75 min. Standard deviation of speed was also measured, and three computerized memory tests were done after the driving task. On treatment day 4, a sleep latency test (SLT) was done before and after the driving test. This was measured by EEG, which has the advantages that it is less sensitive to motivational factors and does not require practice, and base-line values remain stable from one day to the next (4). In terms of EEG readout, a subject's performance can be related to the various types of energies detected; i.e., theta (4–7 Hz) and delta energy (2–4 Hz) are associated with drowsiness/sleepiness, alpha energy (8–13 Hz) with an alert, normal state, and beta energy (14–20 Hz) with an excited or aroused state.

On both test days, triprolidine significantly impaired performance in the driving and psychometric tests, indicating a general lowering of CNS function. This effect was seen even at the low dose of 5 mg twice daily, emphasizing the sensitivity of all the tests used in the study to the sedative effects of this active (reference) control drug. Moreover, the effect of triprolidine was smaller on day 4 than day 1, confirming the reported tolerance of the sedative properties of this drug (5). Terfenadine at a dose of 60 mg twice daily impaired psychometric performance after subchronic treatment; i.e., it showed the potential to impair memory performance and mechanisms relating to memory function. In contrast, neither terfenadine nor cetirizine impaired highway driving or induced daytime sleepiness (6).

This study confirms those which used simulators to study driving performance in the laboratory or on a closed circuit to assess the psychometric effect of antihistamines (7). Gengo et al. (8) did a double-blind, placebo-controlled crossover study with three doses of cetirizine (20, 10, and 5 mg). These workers reported that cetirizine had no effect on mental performance, nor did it cause drowsiness. In contrast, the positive control, diphenhydramine, impaired mental performance and caused drowsiness. In another double-blind, randomized, crossover study, cetirizine and loratadine were compared with placebo for their ability to reduce histamine-induced wheals. In this regard, cetirizine was found to be more potent than loratadine. Neither drug affected subjective assessment of central effects, and cetirizine was devoid of EEG changes. In contrast, loratadine induced slight changes in

EEG recordings (9). Betts et al. compared cetirizine (10 and 20 mg) with terfenadine (60 and 120 mg) for their effects on driving performance. Cetirizine was found to have a slight effect on psychometric function at a dose of 20 mg. In contrast, cetirizine at 10 mg had no effect, nor did terfenadine influence CNS function at either of the doses tested (7). Finally, cetirizine (5, 10, or 20 mg) was compared with hydroxyzine (25 mg) for its ability to induce daytime sleepiness in normal, healthy subjects by EEG, measurement of eye movement, and the multiple sleep latency test. The study was of a randomized, double-blind, parallel-group, placebo-controlled design, and it included 60 men and women. The volunteers spent two nights sleeping in the laboratory before entering the trial to acclimatize them and to standardize EEG readings. Subjects who received cetirizine in any of the three doses did not differ from control subjects given placebo in any measure of daytime alertness. In contrast, for about 4 h after treatment, subjects receiving hydroxyzine were significantly more sedated than subjects given placebo (10).

In a still unpublished report (11), Riedel et al. examined the acute and subchronic effects of terfenadine and loratadine on psychomotor and driving performance. Loratadine (20 mg every day), terfenadine (120 mg twice daily), triprolidine (5 mg twice daily), and placebo were given over 4 consecutive days. Driving tests were conducted on days 1 and 4 of the study, and, in each case, two tests were done at 2 and 4 h after treatment. A total of 376 driving tests was done, and the SDLP and EEG were scored for each case. Of these, 10 were prematurely terminated by the driving instructor. Triprolidine caused six early terminations, terfenadine three, and loratadine one. Fig. 4 shows the average SDLP as a function of drug

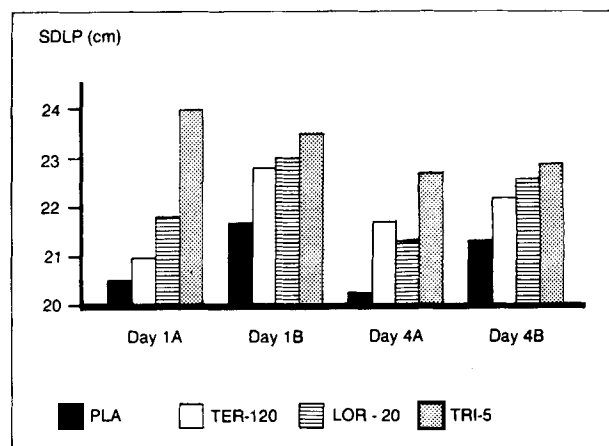


Fig. 4. Average SDLP as function of drug treatment, day of treatment (1 and 4), and time of testing (A and B reflect 2 and 4 h after drug administration, respectively).

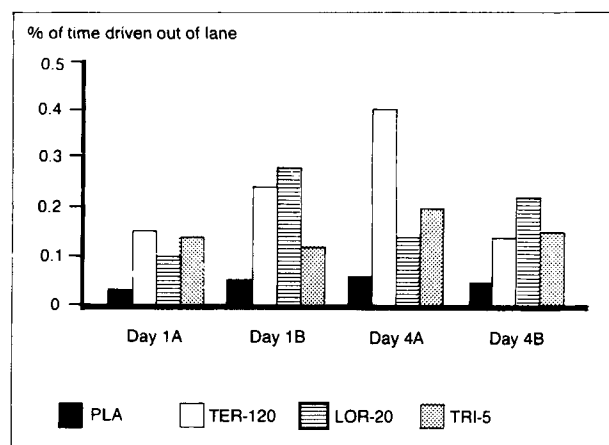


Fig. 5. Average percentage of time spent out of lane as function of drug treatment, day of treatment (1 and 4), and time of testing (A and B reflect 2 and 4 h after drug administration, respectively).

treatment on days 1 and 4 after drug treatment at 2 and 4 h after drug administration. Fig. 5 expresses the data as the percentage of time the car was driven outside the lane. Both loratadine and terfenadine caused statistically significant increases in the mean SDLP.

For both drugs, the SDLP tended to be higher on test day 1 than on day 4. In addition, the SDLP was higher during the second driving test done at 4 h than the earlier test (2 h). The EEG showed that loratadine caused increased alpha and beta energy, and that the drug significantly increased beta energy more in men than women. Triprolidine increased theta energy and both low and high alpha energy. Terfenadine EEG changes were similar to those caused by the other drugs, but these changes did not attain statistical significance. These investigators concluded that both terfenadine and loratadine had the potential to impair driving performance, but the degree of impairment was such as to be of dubious practical relevance. However, this conclusion can be criticized as being an inadequate interpretation of the results of this study. The investigators found that both terfenadine 120 mg twice daily and loratadine 20 mg every day elevated SDLP seriously, and that subjects drove out of lane as a result of drug treatment. They further concluded that triprolidine had the potential to impair driver performance moderately, to a degree greater than that observed with a blood-alcohol concentration greater than 0.5 promille. Continuous EEG monitoring during tests of this nature may lead to a better understanding of behavioral changes induced by antihistamine treatment.

In another study, which also used road driving combined with EEG, cetirizine was compared with

loratadine for effects on actual driving performance of 16 healthy male and female volunteers using a six-way, double-blind crossover design (12). Cetirizine (10 mg) and loratadine (10 mg) were compared with placebo, both in the presence and absence of alcohol (0.72 g/kg). Performance measures included a psychometric test battery. These, and the driving task, were done 2 h after treatment. During on-the-road driving, SDLP was measured together with monitoring by single-lead EEG. As expected, alcohol affected almost every performance measure and altered the EEG energy spectrum. Cetirizine also affected performance, causing a statistically significant variation in speed and SDLP changes of 2 cm, as compared with placebo (Fig. 6). Several cetirizine-placebo differences in subjective feelings and test performance were also significant. Loratadine had no significant effect on any performance measure. This study concluded that cetirizine had the potential to cause mild impairment of performance after a single 10-mg dose. In contrast, another double-blind, randomized, crossover study utilized subjective testing and EEG to compare the peripheral and central effects of cetirizine and loratadine. Neither drug had any effect on the subjective performance tests, and cetirizine was devoid of EEG effects, while loratadine induced slight and limited EEG changes (9). Moreover, simulated assembly line performance was used in a study to assess the psychometric effects of cetirizine, as compared with hydroxyzine or placebo (13). Subjects were trained to a minimum of 80% correction rate for the task before entry into the study. Effects on both subjective and objective performance measurements were consistently seen with hydroxyzine, but not with cetirizine or placebo.

In conclusion, it can be stated that dosage increases beyond those recommended by the manufacturer when giving the new-generation antihis-

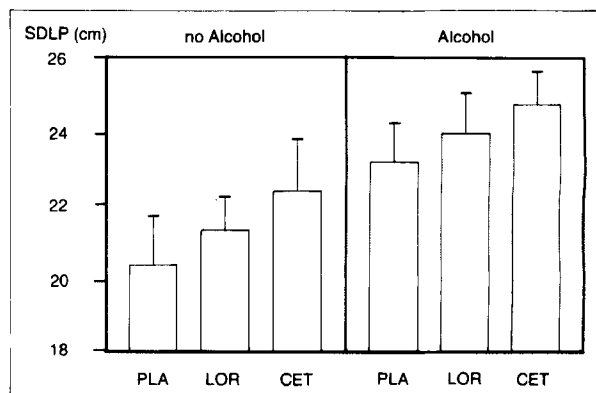


Fig. 6. Comparison of effect of placebo, loratadine, and cetirizine on SDLP during on-road driving in presence and absence of alcohol.

tamines can increase the possibility of impairment of psychometric performance. The difference between the older and newer antihistamines lies in the selectivity of the latter drugs. Measurements of psychometric performance by methods including EEG, laboratory-based skill assessments, and practical tests such as on-road-driving and EEG (the latter two may also be combined) have proven to be very sensitive measures of the CNS effects of antihistamines. These psychometric tests have shown that some of the new-generation antihistamines may measurably affect performance. However, in most cases, these changes are too small to be of practical concern. These medications, including cetirizine, can safely be given to patients who need to continue their normal daily activities, including driving. Finally, the use of continuous EEG testing during psychometric tasks may lead to a better understanding of the behavioral effects of antihistamines.

Round-table discussion

Juhlin: I would like to return to the subject of excitement. If someone is excited and then takes a low-sedating antihistamine, they might perform better in your tests, is that right?

Volkerts: It's possible, but measurement of such a response would be subjective rather than objective.

Rihoux: What is the explanation of the fact that H₁-antagonists tend to induce sedation after acute administration, but this effect is much less after chronic administration?

Volkerts: Do you mean the effect of triprolidine, for example? We know from the literature that both patients and healthy volunteers show some tolerance to triprolidine within 24 h of administration.

Rihoux: So if you start with an immediate sedating event, it then decreases with more chronic administration of the drug. This may be due to the effect of a metabolite and/or some form of accumulation.

Volkerts: It is possible that increasing the dose will result in a higher risk of adverse effects.

Simons: It would help if we understood the mechanism by which sedation occurs. We might then better understand the mechanism for the tolerance that occurs. Ian [Hindmarch], do you have any thoughts on this in the light of your many studies of this problem?

Hindmarch: The only assumption we can make is that the role of histamine in the CNS seems to be related to the maintenance of arousal. So antihistamines have the capacity to interfere with this process, but in what manner nobody knows. What we do know is that there is an effect because we can measure it. I think Ed [Volkerts] has illustrated this very well in his talk. Some antihistamines can affect some individuals profoundly, but we do get subjects who appear to be relatively unaffected. The question I was going to ask was regarding the O'Hanlon et al. study. You referred to the time the car was driven out of the lane; did O'Hanlon include those that dropped out of the study in his calculations?

Volkerts: I don't know? He didn't discuss this point.

Hindmarch: Well, if he didn't, he should have included those that dropped out by performing an end-point analysis on them, because they should be seen on the negative side.

Volkerts: Yes, but the percentage of out-of-lane driving was calculated for the whole group. A subject may spend a proportion of the test driving out of lane, but this would be included in the percentage of time spent driving in lane.

Simons: So some subjects may have started too close to the edge of the lane to begin with?

Volkerts: For example, the difference between the effects of alcohol and drugs regarding driving performance is quite marked. With alcohol, subjects take more risks in their driving, including driving much faster, but they also tend to drive in the middle of the lane. In contrast, when they take drugs, they become more careful and also tend to drive on the inside, i.e., nearer the edge of the highway. In the latter circumstances, they increase the possibility that they will go out of the lane if they do weave.

Hindmarch: Could the tolerance that we can see to antihistamines be due to a defect in the principle of the test? Perhaps the initial position in the lane on the highway will influence the outcome of the test.

Volkerts: But the primary parameter we measure is the SDLP or amplitude of any weaving.

Simons: Tolerance to some antihistamines has been shown in lab-based performance tests as well as in driving tests.

Volkerts

Volkerts: True, and I should emphasize that we train all our volunteers before the test so the effect of these drugs is being tested on skilled behavior. Also the lab-based part of the study design is a balance between lattice square tests and repeated skill-based tasks.

Simons: So what we think of as well-understood effects, i.e., adaption or tolerance to the CNS effects of antihistamines, turns out not to be so well understood at all. For years, right up to the late 1980s in fact, it was said that people develop tolerance to the peripheral effects of these drugs due to metabolism. Recent studies by ourselves and Jean Bousquet have shown that patients do not become tolerant to the peripheral effect of antihistamines.

Hindmarch: We have shown the same sort of thing in studies with tricyclic antidepressants (which are also antihistamines), in that you cannot show tolerance to these drugs in terms of CNS activity.

Simons: So the tolerance is not real?

Hindmarch: Yes, after a time the volunteers stop complaining about side-effects such as a dry mouth and double vision. Yet the effect on their short-term memory is still there because we can measure it. The problem with antihistamines is that people do not respond to them in a consistent manner. This is emphasized by our own work in which different studies have contradicted each other.

Simons: The problem is that the people who are paying the medication bills might seize on the fact that CNS effects are not all that important. In terms of studying changes in the degree of H_1 peripheral blockade over several months, you still see good blocking effects even at the end of such a period. However, with such long-term studies, one problem might involve ensuring patient compliance.

Hindmarch: I agree with your latter point; after all, who of us would like to take triprolidine for 5 days, let alone over 3 months?

Simons: Yes, studies often rely on volunteers who work or are students and therefore need to be alert. So one wonders how compliant they are on a long-

term basis. We know that even in studies looking at good drugs in patients with allergic disorders, a compliance rate of 60% is usual. It could be a great deal less than this for normal volunteer studies. Often compliance hasn't even been monitored in studies in which tolerance to the CNS side-effects of antihistamines was shown to develop.

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