LORATADINE AND ALCOHOL IN COMBINATION:
LACK OF INTERACTION IN AN OPEN ROAD DRIVING STUDY.

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Summary. A two-part investigation of a new antihistamine, loratadine (Clarityne®) was conducted to determine whether the drug is safe for use by patients who drive. This was the expectation based upon earlier pharmacological studies showing that loratadine fails to cross the blood-brain barrier and clinical studies showing that patients generally do not experience sedation under the influence of the drug.

The first part was an acute study, in which the effects of single doses of loratadine 10 and 20 mg, terfenadine 60 mg, triprolidine 10 mg in a slow-release formulation and placebo on driving performance were determined. Driving performance was assessed by means of measuring the driver's road tracking error in a standard open road driving test. Neither loratadine dose nor that of terfenadine significantly affected driving performance relative to placebo, whereas triprolidine did.

The second part was a study, in which the acute and subchronic effects over four days of loratadine 10 mg OD + Placebo OD, terfenadine 60 mg BID and placebo BID with and without alcohol on driving performance were determined.

The results showed that neither loratadine nor terfenadine potentiated the impairing effects of alcohol on driving performance.

On the basis of these investigations results it would seem that loratadine 10 mg O.D. is a safe antihistamine for use by patients who drive.

1. Introduction

Antihistamines (H₁-receptor blockers) are effective in the treatment of allergic reactions such as allergic rhinitis and urticaria. For many years the most widely used drugs, e.g. diphenhydramine, chlorpheniramine, clemastine, promethazine and triprolidine, all possessed unwanted CNS side-effects, especially sedation (Clarke & Nicholson, 1978; Nicholson, 1979, 1984). Recently, new histamine antagonists with few or no effects in the central nervous system, e.g. terfenadine (Cheng & Woodward, 1982), cemetizine, mequitazine (Nicholson & Stone, 1983) and astemizole (Van Wauwe et al., 1981) have been introduced into clinical practice. Other compounds with minimal or no central effects are telemastine (Brown et al., 1986), acrivastine (Cohen et al., 1987), loratadine (Bradley & Nicholson, 1987) and cetirizine (Pechadre et al., 1988). Antihistamines free of sedative effects that cause performance impairment are of great practical relevance since they are preferable for the treatment of patients who engage in safety-critical occupations such as motor vehicle operation (Nicholson, 1985).

Loratadine is an orally effective, long-acting antihistamine devoid of CNS or autonomic effects, both in animals and in man (Barnett et al., 1984; Bedard et al., 1985). Metabolic studies in man with ¹⁴C-loratadine have shown that this
drug is rapidly absorbed but undergoes extensive first-pass metabolism (Katchen et al., 1985). Descarboethoxyloratadine is one of the active products of the loratadine metabolic transformation. However, this metabolite is present in plasma at very low concentrations since it is also extensively metabolized. Single-dose pharmacokinetic studies have shown dose-proportional absorption and an elimination half-life of 8 to 11 hours for loratadine and 17 to 24 hours for descarboethoxyloratadine (Hilbert et al., 1986). These pharmacokinetic properties were also found in a multiple-dose pharmacokinetic study by Radwanski et al. (1987) which supports use on a once-a-day dosage regimen. The manufacturer's recommended daily dose is 10 mg.

Loratadine was found to be free of both CNS-effects and drug-alcohol interaction effects in several laboratory performance studies (Moser & Plum, 1987; Bradley & Nicholson, 1987; Gaillard, 1987). However, this evidence may not be sufficient for indicating that loratadine would be safe for use by patients who drive. The major problem with results obtained using laboratory tests is that they have never been shown to predict performance impairment in actual driving under the influence of drugs (Clayton, 1976; O'Hanlon, 1980, 1982; Silverstone, 1974).

O'Hanlon et al. (1984, 1986) have argued that the best evidence for any drug's safety, short of large-scale drug effect monitoring once it has entered the market, comes from the most realistic performance testing possible; i.e. safety-controlled studies of driving performance in an actual vehicle on real roads in traffic.

2. Experiment 1

Method

Twenty healthy male volunteers were treated on separate occasions with single doses of loratadine 10 mg (recommended daily dose), loratadine 20 mg, terfenadine 60 mg (recommended daily dose), triprolidine 10 mg in a slow-release formulation and placebo. This was done double-blind, according to a cross-over design. One half of the subjects undertook a 1-hour driving test after waiting one hour from the time of drug or placebo ingestion; the other half did the same after three hours.

The driving test consisted of attempting to hold a constant speed (95 km/hr) and steady lateral position between the boundaries of the right (slower) traffic lane while operating a specially instrumented vehicle, under supervision, over a 100 km primary highway circuit (O'Hanlon, 1984). The test vehicle was an extensively modified 1986 Volvo station wagon, with measurement and registration equipment on board in order to record lateral position and speed continuously during the test runs. An index of road tracking error was obtained by means of calculating the standard deviation of lateral position over time.

Results

Three test rides were terminated. One test was terminated at the request of the subject, the other two were terminated by the licensed driving instructor. In all these cases subjects had been administered triprolidine 10 mg (slow release).
Road tracking error or SD lateral position was calculated over all 10 km measurements obtained from each subject in each test. These were partitioned by groups and treatment conditions. Group means and standard errors (SE) of the means were calculated and the results are as shown in Figure 1.

The results of multivariate analysis of variance showed a significant difference in SD lateral position between treatment conditions \( (F=4.63; \ df=4,15; \ p<.01) \). The difference between groups experiencing 1- and 3-hour waiting periods was not significant, nor was the interaction between conditions and groups.

The significant multivariate difference between conditions was entirely due to the effect of triprolidine on both groups' performance: Univariate tests showed that triprolidine produced elevated SD lateral position relative to placebo, in both the 1-hour and the 3-hour waiting groups \( (F=15.20; \ df=1,18; \ p<.0001) \).

### 3. Experiment 2

**Method**

Sixteen healthy male volunteers received three separate treatments consisting of multiple loratadine (10 mg, O.D. + placebo OD), terfenadine (60 mg B.I.D.) and placebo (B.I.D.) doses over four consecutive days. This was done double-blind, according to a cross-over design. Subjects were tested twice on Days 1 and 4 in each treatment series, half in the morning and half in the evening. The first test occurred one hour after drug or placebo ingestion. The second occurred about 90 minutes later, after ingestion of an alcohol dose sufficient to raise blood alcohol concentration to about .094 g % (peak), which declined on the average from .066 g % to .036 g % during the test.

**Results**

All subjects completed the tests after the drug or placebo but without alcohol. No subject voluntarily terminated any test, but 10 tests were terminated by the experimenter because of poor driving performance of subjects treated with alcohol. Two subjects were stopped three times in different tests, one subject twice and two subjects once. There was no indication that any factor besides alcohol was responsible for the subjects' poor driving or the decision to stop the test.

An average SD lateral position value was calculated over all 10 km measurements obtained from each subject in each test. These were partitioned by treatment condition, day of treatment and absence/presence of alcohol. Group means and standard errors of the means were calculated and the results are shown in Figure 2. The only obvious effect is that of alcohol: regardless of the group or condition, the subjects drove worse after alcohol and consistently so whenever tested. Individual SD lateral position values were analyzed by MANOVA. The factors tested were treatment conditions, day of treatment, absence/presence of alcohol, time of testing and their interactions. The effect of treatments was not significant. The effect of alcohol was highly significant \( (F=120.75; \ df=1,14; \ p<.0001) \). The presence of alcohol led to a mean increase in SD lateral position of 5.3 cm (absence of alcohol: 22.2 cm; presence of alcohol: 27.5 cm). Furthermore, the subjects did not compensate for their poorer road tracking performance under the influence of alcohol, in a safe
manner. The average speed was also significantly (F=30.86; df=1,14; p<.001) higher (absence of alcohol: 99.5 km/h; presence of alcohol: 101.6 km/h). Their average lane position significantly (F=11.35; df=1,14; p<.005) shifted to the left of centre, i.e. closer to overtaking vehicles (absence of alcohol: 2.5 cm left of centre; presence of alcohol: 5.7 cm left of centre).

4. Discussion

Both studies provided evidence that terfenadine and loratadine are antihistamines that can safely be used by patients who drive. In the Acute Study neither a single dose of 60 mg terfenadine nor of 10 mg or 20 mg loratadine had any effect on driving performance as measured in the standard, road tracking test. Triprolidine 10 mg (slow releasing) caused the subjects to drive with greater road-tracking error as measured by an elevated SD lateral position.

Several important results emerged from the Subchronic Study. Neither loratadine 10 mg OD nor terfenadine 60 mg BID had any effect on driving performance during the 1st treatment day, confirming the results of the Acute Study. Neither drug had any effect on the 4th treatment day when the subjects' plasma concentrations should have reached pharmacological "steady state". Alcohol had adverse effects on driving performance. The subjects did not compensate for their elevated SD lateral position by shifting the vehicle's mean lateral position toward the right. On the contrary, they significantly shifted the vehicle's mean position to the left (i.e. closer to possibly overtaking vehicles). They also drove slightly, though significantly, faster.

The most important result was not that a moderate dose of alcohol produces driving performance impairment, but that the combined effects of alcohol and either of the antihistamines were no greater than alcohol's alone. This was true for both loratadine and terfenadine, administered in recommended daily doses, acutely and after repeated doses. In no case was there any indication that either drug potentiated alcohol's effect.

References


