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Effects of Lorazepam on Psychomotor Performance: A Comparison of Independent-Groups and Repeated-Measures Designs

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FILE, S. E. *Effects of lorazepam on psychomotor performance: A comparison of independent-groups and repeated-measures designs.* PHARMACOL BIOCHEM BEHAV **42**(4) 761-764, 1992.—The purpose of this study was to compare the sensitivity to the effects of lorazepam (2.5 mg) of a design using independent groups (random allocation of subjects to either a placebo or a lorazepam treatment) with a repeated-measures design (subjects tested both before and after lorazepam treatment). With both designs, it was possible to demonstrate significant and equal effects of lorazepam in tests based upon speed of responding: Lorazepam significantly increased simple reaction time and significantly decreased performance in number cancellation and symbol copying tasks. The independent-groups design was more sensitive (i.e., showed effects at a higher level of significance) to the lorazepam-induced impairment in episodic memory, as assessed in a picture recognition task, and to the lorazepam-induced impairment in a word completion task. Comparisons between the two control condition scores indicated that there were unlikely to be significant group differences with random allocation of a relative homogenous group of volunteers, such as medical students. While either design would be appropriate for homogeneous populations, for a heterogeneous clinical population where groups cannot be matched the repeated-measures design would be preferable.

Benzodiazepines Sedation Memory Experimental design

THIS article addresses the question of the relative reliability and sensitivity of an independent-groups vs. a repeated-measures design for assessing the psychomotor effects of benzodiazepines. The use of an independent-groups design is widespread in behavioural pharmacology (3,5-7,14-16) and experimental psychology, but there are two potential concerns. The first is that despite random allocation of subjects to experimental groups differences between groups might exist prior to any drug administration. This experiment will provide the opportunity of comparing the undrugged scores of the two groups of eight medical students; the results of the present study can also be compared with scores obtained by another group of 10 students tested undrugged 12 months earlier under the same test conditions (12). Perhaps a more serious restriction from the use of an independent-groups design is the potential loss of sensitivity (as defined by statistical significance) compared with a repeated-measures design. This experiment therefore compared the sensitivity to the effects of lorazepam of comparisons made between two independent groups (one treated with placebo and one with lorazepam) and that made between pre- and postdrug measurements on the same subjects.

The drawbacks that arise from the use of a repeated-measures design are of a different nature. Above all, the design relies on no, or only minimal, practice effects in the tasks selected. This is often quite difficult to achieve, particularly in a clinical setting, where it is seldom possible to give subjects sufficient prior test experience to remove any subsequent practice effects. Ideally, a cross-over design should be used in which each subject is tested under both placebo and drug conditions but in which the order of testing is counterbalanced (2,4,10,11). However, this is not always possible: Volunteers are often unwilling to come on two separate test occasions, and in clinical studies one is often restricted to testing patients prior to and then after drug administration (1,14,18). In this case, test order is confounded with drug treatment and, with longer test sessions, the effects of fatigue and boredom (as well as possible practice effects) have to be considered. To control for this, it is necessary to test two independent groups (one placebo, one drug treated) both before and after any tablet is administered. This last solution (a between-within design) is the most labour intensive and leads to long test sessions.

The present experiment focused on a comparison of an independent-groups and a repeated-measures design using conditions known to be free of the effects of practice and fatigue. We therefore selected tests in which two sets of matched difficulty were available. We used a relatively homo-

geneous population of subjects, medical students who were naive to all the tests, and a short (15 min) test session. A pilot experiment on a group of undrugged subjects confirmed that there was no change in performance on any test when subjects were tested on two occasions 2 h apart. Eight subjects were allocated to each experimental group (placebo, lorazepam, pre-post) and none of the subjects or the experimenter knew whether a placebo or active tablet was being administered. Subjects in the pre-post group were aware that they were tested prior to administration of a tablet but were told the tablet might be lorazepam or placebo. Lorazepam (2.5 mg) was selected since it was known to change performance in all tests selected.

Three tests based upon speed of responding were selected: number cancellation, symbol copying, and simple reaction time. These tests are all sensitive to the sedative effects of benzodiazepines (8,11). In addition a test of recognition memory was used to assess lorazepam's effects on explicit, episodic memory (13). Finally, a word completion task that draws on semantic memory was included. This task has previously been found sensitive to lorazepam's effects (8).

METHOD

Subjects

Subjects were 24 (12 male, 12 female) medical students at United Medical and Dental Schools of Guy's and St Thomas's Hospitals, aged 20–22 years. They were healthy and medication free at the time of testing and gave informed written consent prior to any drug administration. They were randomly allocated, eight (four males, four females) to each of the following three groups: placebo, lorazepam, pre-post. Those in the independent groups were tested once only, after the appropriate treatment. Those in the pre-post group were tested both before and after lorazepam administration. Subjects were allowed their normal breakfast but no further food, alcohol, or caffeine-containing beverages before they took part in the experiment.

Drug

Lorazepam (2.5 mg Ativan) and matched placebo tablets were kindly supplied by Wyeth. They were administered with water 2 h before testing began. Administration of tablets and testing of subjects was conducted by an experimenter who did not know which tablets were active and which were placebo. Subjects remained in the laboratory until testing started and were allowed to read or watch television.

Procedure

Subjects were randomly allocated among the three groups with the constraint that there were equal numbers of males and females in each group. Subjects were individually tested and drug administration took place at 1100 h. Subjects were tested in an order randomised between the three groups. The order in which tests were given was the same for all subjects and the tests are described in the order in which they were given. There were two matched versions of each test. Half the subjects in the placebo and lorazepam groups received Sets A and the other half received Sets B. Half the pre-post group received Set A predrug and Set B postdrug; the other half received Set B then Set A. Subjects in the pre-post group were tested prior to administration of any tablet and 2 h after lorazepam administration.

Presentation of Slides

A set of 40 coloured slides (of objects, paintings, abstracts, and architecture) were presented at the rate of 1 every 3 s. Subjects were told to try and remember then and had to reply "yes" to indicate that they had seen each slide. The slide sets had been used in previous studies (8).

Number Cancellation

Two sheets of random numbers were given to subjects. They were asked to cancel all the number 3's on the first sheet and all the number 1's on the second. They were given 90 s for this task. This task has previously shown impairments after 2.5 mg lorazepam (9). The number correctly completed and the number of omissions were scored.

Symbol Copying

Subjects were given a sheet of 10 rows of 25 symbols and asked to copy each symbol in the box below. After a practice of 10 symbols, they were allowed a further 90 s to complete as many as possible. This test was devised by Kornetsky et al. (17) as a control for the speed of performing the motor components of the digit-symbol substitution test. The number correctly completed was scored.

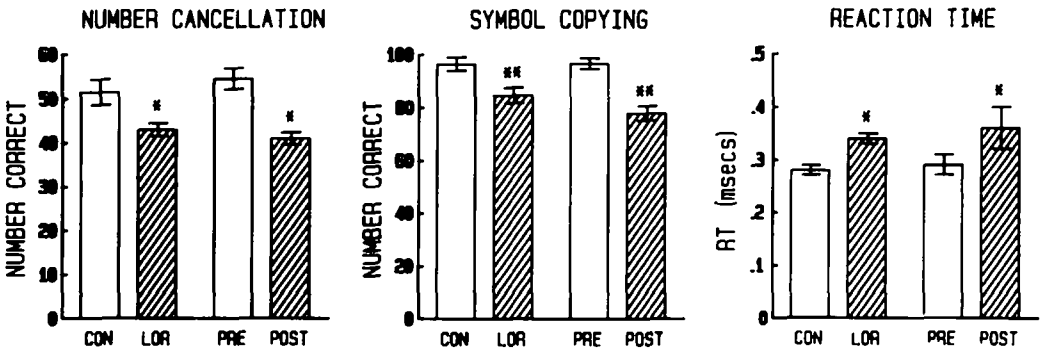

FIG. 1. Mean (±SEM) number of correct responses in number cancellation and symbol copying tasks and mean (±SEM) reaction time (milliseconds) for subjects treated with placebo (CON) or lorazepam (2.5 mg, LOR) or tested before (PRE) and after (POST) lorazepam (2.5 mg). $*p < 0.05$, $**p < 0.01$ compared with control group or pretreatment score, as appropriate.

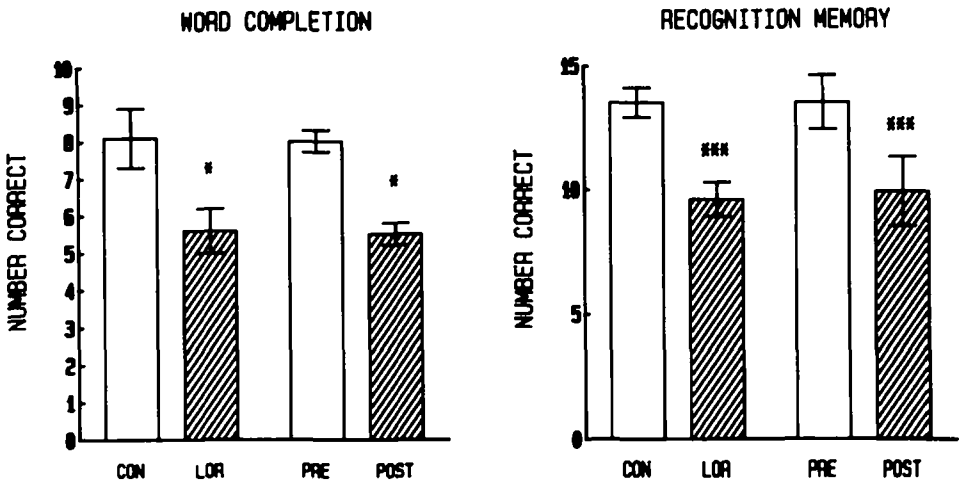

FIG. 2. Mean (± SEM) items correct in word completion and recognition memory tasks for subjects treated with placebo (CON) or lorazepam (2.5 mg, LOR) or tested before (PRE) and after (POST) lorazepam (2.5 mg). $*p < 0.05$, $***p < 0.01$ compared with control group or pretreatment score, as appropriate.

Reaction Time

Subjects were instructed to press the space-bar on a computer keyboard as rapidly as they could in response to the stimulus "yes" that appeared on the computer screen. The reaction time was recorded by an IBM computer. Twenty-five stimulus presentations were given with an intertrial interval randomised between 1 and 10 s. This task was similar to the simple reaction time task used previously to detect the effects of lorazepam and propranolol (11). A mean reaction time was calculated for each subject, excluding times of >700 ms since these were considered outside the normal range and indicated a missed signal.

Word Completion

Twenty-four incomplete words (with three of seven letters missing) were presented to subjects and they were given 2 min to complete as many as possible in any order. The number of words correctly completed was scored. This test has previously been found to be sensitive to the effects of lorazepam (8).

Slide Recognition Test

Subjects were presented with a set of 80 randomised slides, 40 from the original set and 40 new slides. They were required to respond "yes" or "no" according to whether or not they remembered seeing them previously.

Statistics

The data for the independent-groups design were analysed by a one-way analysis of variance (ANOVA) for independent groups. The data for the repeated-measures design were analysed by a one-way ANOVA for repeated measures.

Errors of omission and false positives were scored for each test, but these were extremely low and were not different between the groups. Therefore, the only data presented are the number of correct responses.

RESULTS

Number Cancellation

Comparing the performance of the placebo and lorazepam groups, lorazepam significantly reduced performance in this task, $F(1, 14) = 6.7$, $p = 0.02$. A similar impairment was found in the pre-post group, $F(1, 7) = 7.0$, $p = 0.03$; see Fig. 1.

Symbol Copying

Comparing the placebo and lorazepam groups, lorazepam significantly reduced the number of symbols copied, $F(1, 14) = 8.7$, $p = 0.01$, and a similar impairment was seen in the pre-post group, $F(1, 7) = 12.4$, $p = 0.01$; see Fig. 1.

Reaction Time

Lorazepam significantly increased reactions times [for independent groups, $F(1, 14) = 5.0$, $p = 0.04$; for the pre-post group, $F(1, 7) = 8.7$, $p = 0.02$]; see Fig. 1.

Word Completion

Lorazepam significantly decreased the number of words correctly completed [for independent groups, $F(1, 14) = 5.6$, $p = 0.03$; for pre-post group, $F(1, 7) = 5.6$, $p = 0.05$]; see Fig. 2.

Slide Recognition

Lorazepam significantly impaired episodic memory as measured by the number of slides correctly recognised [for independent groups, $F(1, 14) = 18.3$, $p < 0.001$; for pre-post group, $F(1, 7) = 25.1$, $p < 0.002$]; see Fig. 2.

DISCUSSION

The effects of lorazepam reported in this study are neither new nor surprising. However, the study has revealed an equal sensitivity, as defined by statistical significance, of independent groups of $n = 8$ per group and repeated measures on a group of eight with regard to lorazepam's effects on the tests based upon speed. On the tests of episodic and semantic memory, the independent-groups design showed greater sensitivity, reflected in higher significance levels. Although the independent-groups design involves twice as many subjects, the testing times in the two designs were identical. From the point of view of sensitivity to lorazepam's sedative effects, neither de-

sign has any advantage over the other, whereas the independent-groups design may be preferable for detecting amnesic effects.

A comparison of the scores of the two control conditions (placebo group and predrug scores) reveals very little difference between the two groups of undrugged subjects. Furthermore, these scores are very close to those found in a group of 10 medical students tested 12 months earlier on the same tests (12). It therefore seems most unlikely that significant group differences will arise by chance when a relatively homogeneous group of subjects are randomly allocated to independent groups. However, with a very heterogeneous clinical population unless matched groups can be obtained from previous test scores a repeated-measures design would be preferable.

A comparison of the scores of the two lorazepam conditions also confirms that under these particular test conditions (a brief session, use of matched versions of tests) there was no indication of a change on repeated testing. This suggests that in clinical situations where only a pre-post drug administration design is possible, and where ethical and practical considerations exclude the possibility of placebo treatment, it should be possible to use pilot experiments on undrugged volunteers to determine test conditions in which the effects of practice and/or fatigue are minimal.

In conclusion, certainly as regards the psychomotor effects of lorazepam there seems to be no reason for preferring a repeated-measures over an independent-groups design. Ideally, a repeated-measures design should counterbalance test order and drug treatment. In clinical situations where this is impossible, the confounding effects of test order can be minimised by conducting careful pilot experiments on undrugged volunteers.

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