

Effect of Hydroxyzine on Attention and Memory

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A single intake of hydroxyzine 50 mg was compared to placebo, with lorazepam 2 mg as a verum, in a double-blind, triple-crossover trial. Each of the nine volunteers was tested on three different days, once under each condition. At 2 h after drug intake all volunteers were assessed or reassessed for attention, immediate and delayed (30 min) memory, cognitive ability and subjective feelings of anxiety and fatigue. While hydroxyzine 50 mg and lorazepam 2 mg produced a comparable level of sedation, only hydroxyzine preserved memory and attention. The testing methods were sufficiently sensitive to demonstrate clear deficiencies in attention and short-term and long-term memory with lorazepam. Subjects became somewhat stressed under both sedative treatments because they feared losing their cognitive abilities. Subjects had fewer complaints under hydroxyzine than under lorazepam.

KEY WORDS—Hydroxyzine, lorazepam, attention, memory, sedation.

INTRODUCTION

Hydroxyzine, an H₁-antihistamine, has been in worldwide use for 30 years and has established itself as a proven anti-anxiety and anti-stress agent (Shallowitz, 1956, 1961; Breslow, 1968; Rickels *et al.*, 1970; Goldberg and Finnerty, 1973) with a good record of efficacy and safety (Brunton, 1957; King and Howell, 1966; Gillatt *et al.*, 1985). Although hydroxyzine is chemically unrelated to benzodiazepines, for certain indications they have overlapping uses, e.g. in the treatment of anxiety, as premedication prior to surgery (Desjardins *et al.*, 1981; Herr *et al.*, 1982), and in the management of drug withdrawal (Knott and Beard, 1967).

Many studies on the psychological effect of benzodiazepines have been conducted in normal subjects (Goldberg, 1984). Several studies deal with the effect of benzodiazepines on memory and psychomotor functioning (Giurgea *et al.*, 1982; Curran, 1986; Subhan *et al.*, 1986). Most benzodiazepines tend to have a detrimental effect on tasks involving memory and psychomotor functioning. In clinical practice this effect is highly undesirable, since it further reduces the coping abilities of the anxious patient, whose anxiety is often the expression of his inability to cope.

Hydroxyzine did not affect memory in animal studies (Giurgea *et al.*, 1988; Porsolt *et al.*, 1984; Porsolt and Lenegre, 1988). This study was undertaken in an attempt to investigate the effect of hydroxyzine on memory and attention in man.

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METHODS

Subjects

Nine young, healthy volunteers, five men and four women, participated in the study. They were between 21 and 29 years old (mean age 24.6). All had finished high school. Their anxiety level, as measured by the STAI-DY 2 form was normal.

Treatments

Hydroxyzine 50 mg was compared with placebo, and lorazepam 2 mg was used as a verum. All drugs were presented in identical capsules and were administered in a single intake in the morning.

Design

The study design was a double-blind, triple-crossover comparison of a single intake of hydroxyzine 50 mg, lorazepam 2 mg and placebo, according to a 3 x 3 Latin square design. Thus each subject was tested on 3 different days, 1 day for each experimental dose, with at least 3 days interval.

Assessment and measures

Psychometric assessment of the primary variables, i.e. short- and long-term memory and attention, was undertaken 2.5 h after drug intake. The effect of the medication on anxiety level, mood, sedation,

and relaxation as secondary variables was evaluated prior to administration and 2.5 h after administration.

A modified version of the **15 words of Rey** was used to measure verbal memory. A list of 15 words was read to each subject at a rate of one word every 2 s. Immediately after the word list had been read, the subject recalled orally all the words that he could remember. This procedure was repeated three times. Delayed recall was measured 30 min later. Between immediate and delayed recall, rehearsal of the word list was prevented by presenting the subjects with a battery of questionnaires. When given instructions for the immediate recall test, subjects were informed that they would be later tested on what they still remembered of the word list. Immediate and delayed recall were measured as the absolute number of words remembered after no delay and after a 30 min delay, respectively.

Three different but standardized parallel lists were used in the three experimental conditions.

The Digit Symbol Substitution Test (DSST) (subtest of the WAIS) (Stinissen *et al.*, 1980) was included to evaluate attention and psychomotor performance. The subjects were given 90 s to fill in as many empty squares as possible with the number corresponding to the symbol of the square involved. The raw score is the absolute amount of numbers that the subject matched with the corresponding symbols. Different equivalent versions were used in the three experimental conditions.

Anxiety level, mood, sedation and relation were measured with several self rating scales. The Profile of Mood States (POMS) (McNair *et al.*, 1971–1981) was of interest because of the following subscales: tension–anxiety, vigour–activity and fatigue–inertia. The State Trait Anxiety Inventory (STAI-DY 1) (Spielberger *et al.*, 1983; van der Ploeg *et al.*, 1979) was used during the experiment to evaluate anxiety changes. Ten centimetre Line Analogue Rating scales (LAR) were employed to rate perceived sedation. Each scale was presented twice to every subject during each experimental condition, once before drug intake and once 3 h later. Each time the subject was asked to indicate how he or she felt at that moment.

RESULTS

Complete data were obtained from all subjects under all treatment conditions. The data were analysed using an ANOVA for repeated measurements. In this statistical model two factors were

added to the subject factor: (1) a drug factor which tested the overall difference between the three different drug conditions, (2) a group factor which tested the influence of the sequences of taking the drugs and which validated the design in case of non-significance. Three groups were defined depending on the first drug taken.

When the overall drug factor was statistically significant a contrast analysis was performed to test the differences between hydroxyzine and placebo, and between lorazepam and placebo.

When a pre-drug value was available the variance analyses were performed on the difference between the pre- and post-values.

The sequence of drug intake had no influence on the results of the tests; hence only the probability figures of the contrast analysis are given below.

Both hydroxyzine and lorazepam induce, in comparison with placebo, a feeling of sedation: there is a significant difference between hydroxyzine and placebo on the concentration subscale (0.02) and the dynamics subscale (0.0003) of the LAR, and on the fatigue–inertia subscale (0.0001) and the confusion subscale (0.04) of the POMS. Lorazepam is significantly different from placebo on the LAR scales: concentration (0.02) and dynamics (0.007), while the mentioned POMS scales show a change in the same direction, but this is not significant.

Both hydroxyzine and lorazepam tend to increase, slightly, anxiety (STAI-DY1): hydroxyzine versus placebo = 0.04, lorazepam versus placebo = 0.8 (trend).

Table 1 and Figure 1 summarize the findings on memory. No memory impairment compared to placebo was found following an acute dose of hydroxyzine 50 mg. Neither immediate nor delayed recall was affected. By contrast, under lorazepam 2 mg an overall memory impairment was observed. The impairment in delayed recall was very pronounced and consistent among all subjects. Under lorazepam, subjects reached their maximum performance in immediate recall during the second trial.

The digit symbol substitution test showed no significant psychomotor impairment for the hydroxyzine condition (0.32), in contrast to the lorazepam condition (0.005) (see Figure 2).

DISCUSSION

At the given dose both drugs showed a comparable sedative effect. According to the questionnaires, subjects felt tired, weary and drained of energy. However, while under lorazepam subjects felt

Table 1.

Products	Immediate recall after trials				Delayed recall	
	1st	2nd	3rd	Total	after 30 min	Percentage of words lost after 30 min
<i>Hydroxyzine</i>						
Mean	7.22	10.11	11.44	14.11	9.67	32%
SD	1.09	1.69	2.07	0.93	2.92	17%
<i>Lorazepam</i>						
Mean	5.78	8.56	8.67	12.33	5.33	59%
SD	1.99	2.19	2.00	2.00	2.92	17%
<i>Placebo</i>						
Mean	7.44	10.22	11.00	14.11	9.44	32%
SD	1.42	2.11	1.87	0.78	2.35	14%
<i>Lorazepam/placebo</i>						
	0.02	0.08	0.06	0.07	0.008	0.008
	Sign.	Trend	Trend	Trend	Sign.	Sign.
<i>Hydroxyzine/placebo</i>						
	0.45	0.77	0.63	1.00	0.74	0.52
	NS	NS	NS	NS	NS	NS

This table shows: the mean, SD, and probability levels of the number of words recalled by the nine volunteers on the 1st, 2nd and 3rd trials, the total number of words named at least once over all three trials, and the delayed recall. The percentage of words lost in delayed recall was compared to the total immediate recall.

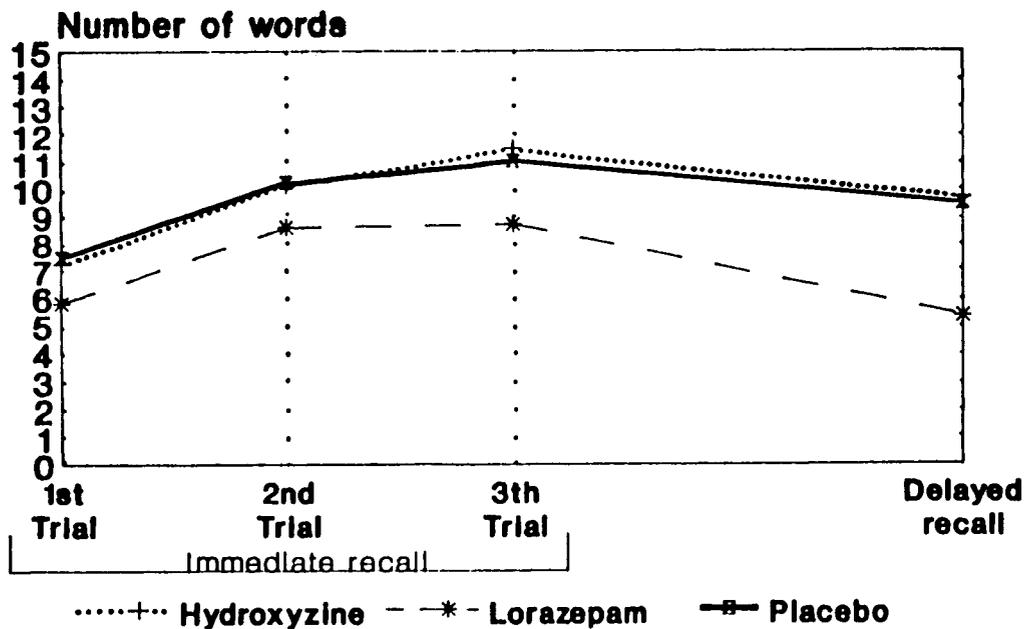


Figure 1. Visualisation of the average number of words remembered

unable to regain control, the same subjects under hydroxyzine felt capable of being attentive and performing when asked. Under lorazepam eight out of nine subjects mentioned disturbed movement control and problems with balance. These complaints were never mentioned under hydroxyzine.

According to the anxiety level of the subjects, the results on the STAI were surprising. Since both active drugs are known as anxiolytics, anxiety reduction could be expected, but the opposite happened. This effect may be due to the fact that we were dealing with a group of healthy volunteers with a normal baseline anxiety level and a strong motivation to perform on the tests as well as possible. We can suppose that, when given sedative drugs, these subjects would feel anxious about losing control. The subjects' comments support this hypothesis.

Hydroxyzine did not affect memory span, either in short-term memory or long-term memory. The fact that on the first repetition there is no difference between the number of words remembered under hydroxyzine and placebo, compared to fewer words with lorazepam, is proof that hydroxyzine causes

no attention deficit or impairment of immediate memory.

With lorazepam there is no increase in the amount of words remembered in the third trial as compared to the second. This can be defined as a deficit in learning through repetition. Such deficit is not found under hydroxyzine. These factors—attention, immediate memory and learning through repetition—are important aspects of overall memory (Israel, 1985). Thus there was no memory impairment whatsoever when hydroxyzine was the memory impairment was observed with lorazepam (Roth *et al.*, 1980; Scharf *et al.*, 1983; Mac *et al.*, 1985; Kumar *et al.*, 1987; Preston *et al.*, 1988). Hydroxyzine does not influence performance on the DSST, in contrast to lorazepam. To fulfil this task, subjects test medication but, as expected, significant rely not only on attention and psychomotor speed but also on memory. If one can memorize the different digit/symbol combinations while doing the test one can proceed faster, since there is no need to repeatedly check the code on top.

The present findings taken as a whole show that an acute dose of hydroxyzine 50 mg, in spite of

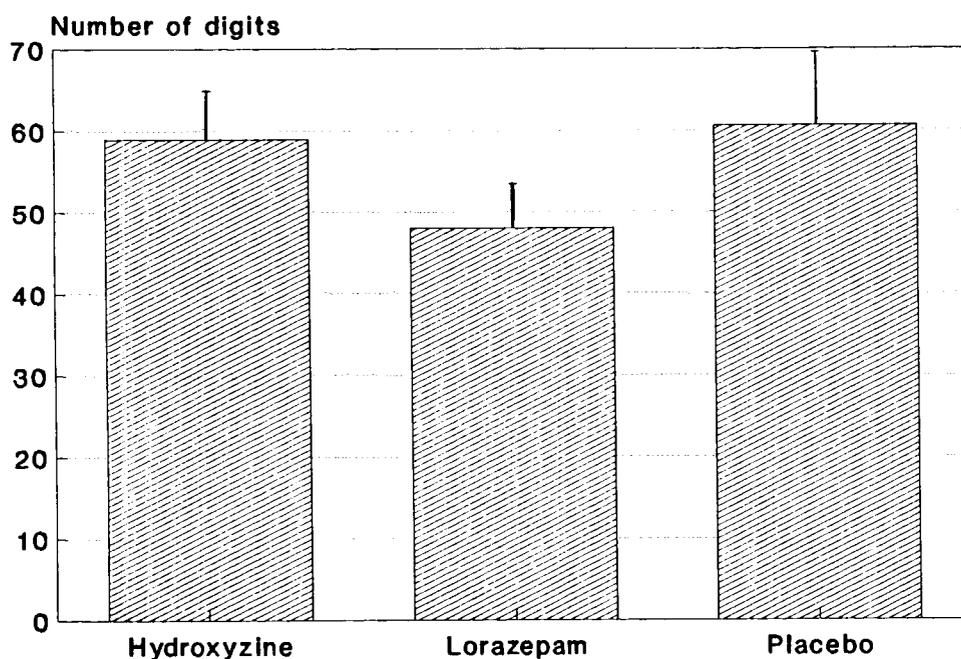


Figure 2. Mean and SD over all three experimental conditions on the DSST. Contrast analysis on these data gives the following results: Lo/P10-005; Hx/P10-32

an important sedative effect, has no consequent effects on either memory, attention or psychomotor performance.

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