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The psychopharmacological effects of premazepam, diazepam and placebo in healthy human subjects

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1 Pharmacological studies of premazepam in animals predicted antianxiety activity without sedation and, in combination with diazepam, a reduction in the sedative effects of the latter.
2 The effects of single doses of premazepam (25 and 50 mg), diazepam (10 mg), premazepam (25 mg) plus diazepam (10 mg), and a placebo on subjective feelings, psychological tests and the EEG were studied in a double-blind cross-over study in 10 healthy subjects.
3 In a repeated dose study in eight subjects, the effects on subjective feelings, psychological tests and the EEG of premazepam (5 and 10 mg twice-daily), diazepam (5mg twice-daily) and a placebo were compared.
4 Premazepam had a different EEG profile from diazepam, producing more slow and less fast wave activity. In the single dose study its effects were similar to diazepam for sedative action and most of the psychological tests, with a tendency towards greater psychomotor impairment. In the repeated dose study, however, premazepam caused less sedation and also tended to produce less psychomotor impairment.
5 The combination dose of premazepam (25 mg) plus diazepam (10 mg) in the single dose study indicated an additive effect rather than an antagonistic one.

Keywords premazepam diazepam electroencephalogram sedation psychological impairment

Introduction

Premazepam, or 3,7 dihydro-6, 7-dimenthyl-5-phenyl-pyrrolo-[3,4-e] 1,4-diazepine-2(1H)-one, is a pyrrolodiazepine which binds *in vitro* and *in vivo* to benzodiazepine receptors (Vitiello *et al.*, 1983). Pharmacological studies of premazepam in animals predicted that its administration to humans would produce an anxiolytic effect without sedation. Premazepam is active in conflict behaviour tests, in taming aggressive monkeys, and in preventing stress induced increase of serum corticosteroids. It is inactive in impairing psychomotor performance in the rota rod test in both rat and mouse, in inducing sleep in the midpontine pretrigeminally-transected cat, and is weakly active in impairing the righting reflex in the rat. Furthermore, its animal pharmacology is particularly interesting and unusual in that it has an antagonistic effect on diazepam, counteracting its CNS depressant effects, which suggested that in combination with diazepam it might reduce the sedative effects of diazepam in humans.

The present investigations were carried out to compare the effects of premazepam with those of diazepam and a placebo on a variety of measures previously shown to be sensitive to the

administration of benzodiazepines. Itil *et al.* (1983) found 25mg premazepam to be the lowest single dose to elicit clear-cut CNS effects of an anxiolytic type, with the optimal single therapeutic dose lying between 25 and 50 mg. In the single dose study 25 mg and 50 mg premazepam and a combination dose of 25 mg premazepam plus 10 mg diazepam were compared with 10 mg diazepam. The repeated dose study compared 5 mg and 10 mg premazepam twice-daily with 5 mg diazepam twice-daily over a period of 1 week. The findings of the single dose study suggested that the relatively lower doses of premazepam to diazepam in the repeated dose study would be more equivalent and better tolerated.

Methods

Approval was obtained from the Ethical Committee (Research) of the Institute of Psychiatry and all subjects gave informed consent. The subjects were instructed to arrive fasted from the night before on each test day and not to drink alcohol for 48 h preceding the test day itself. They were allowed a light meal after the drug had been absorbed. Testing began at the same time in the early morning for each subject. The use of CNS drugs during the trial was not permitted.

Self-ratings

Mood rating scale Feeling at the time of each testing was measured on a series of sixteen analogue scales. This mood rating scale has been subjected to a principal component analysis which yielded three factors (Bond & Lader, 1974). The first factor is one of *alertness* and consists of nine of the scales: alert-drowsy, strong-feeble, muzzy-clear-headed, well coordinated-clumsy, lethargic-energetic, mentally slow-quick-witted, attentive-dreamy, incompetent-proficient and interested-bored. The second factor measures *contentedness* and the five scales which load on it are: contented-discontented, troubled-tranquil, happy-sad, antagonistic-amicable and withdrawn-gregarious. The third factor, *calmness*, is composed of two scales: calm-excited and tense-relaxed. On each scale, the subject marked the point along a 100 mm line that represented how he felt.

Bodily symptom scale A similar scale has been constructed to measure bodily symptoms. It has 14 items concerning side-effects which have been reported after diazepam: anxiety, sweating, shaking or trembling, palpitations, nausea or sickness, loss of appetite, dryness of mouth, muscular tension, irritability, physical tiredness, headache, dizziness and indigestion or stomach trouble. The subject rated them along a 100 mm line between absent and severe.

Physiological measures

Electroencephalogram The EEG was recorded from vertex and left temporal electrodes (Bond & Lader, 1972). It was analysed by broad waveband analysis into four parallel band-pass filters with upper and lower frequencies set as follows: (1) 2.4–4 Hz; (2) 4–7.5 Hz; (3) 7.5–13.5 Hz; (4) 13.5–26 Hz. The outputs of these four filters were fed into four analog-to-digital converter inputs of a PDP-12A computer. Thirty two 5 s epochs of EEG were analysed for two conditions; eyes open and eyes closed. The EEG samples were monitored visually on the computer's screen and artefacts were eliminated by excluding 'noisy' samples from the analysis. The mean rectified voltage in each waveband was calculated. No subjects were excluded from the study on the basis of their pre-drug EEG patterns.

Psychological measures

Tapping rate The subject tapped a key as quickly as possible for 60 s. The mean inter-tap interval was calculated.

Digit symbol substitution test This is a subtest of the Wechsler Adult Intelligence Scale (WAIS) involving coding skills. The score was the number of symbols correctly substituted for numbers in 90 s.

Single dose study

Subjects, drugs and experimental design Ten normal healthy male volunteers aged between 23 years and 37 years took part in the study. Comparisons were carried out between two doses of premazepam (25 and 50 mg), diazepam (10 mg), premazepam (25 mg) plus diazepam (10 mg), and a placebo. The subjects were given three identical looking white capsules on each occasion. Each subject was tested on five separate occasions at 2-weekly intervals. The drugs were assigned according to two 5 × 5 Latin square designs and the conditions were double-blind. The subjects were tested before each drug and at 1h, 3h and 5h after each drug.

Analysis of data A four-way analysis of variance was calculated, the main sources of

variance being subjects, drugs, occasions and times. Differences between drugs were obtained from the drugs × times interaction. Ten subjects, five drugs and five occasions allowed two Latin squares within the cells of which each subject was tested four times. The following contrast analyses were computed: (a) placebo *vs* active drugs; (b) diazepam (10 mg) *vs* premazepam (25 mg and 50 mg); (c) active drugs *vs* premazepam (25 mg) plus diazepam (10 mg); and (d) premazepam (50 mg) *vs* premazepam (25 mg). Only results which show the drugs to have a significantly different effect from placebo or from each other are reported. As *a priori* contrast analyses have been carried out in preference to post hoc testing, no indication of critical differences for individual points is given in the graphs.

Repeated dose study

Subjects, drugs and experimental design Eight normal healthy male volunteers aged between 22 years and 47 years took part in the study. The subjects were given four 1-week treatments with a minimum 'wash-out' interval of 3 weeks between each drug. They were tested on day 1 and day 8 of each of the four treatment periods. Two doses of premazepam (5 and 10 mg twice-daily) were compared with one dose of diazepam (5 mg twice daily) and a placebo (two capsules twice-daily). The premazepam, diazepam and placebo were formulated as identical white capsules. The subjects were given a supply of envelopes on day 1 with sufficient capsules to last until day 8. The drugs were assigned according to two 4 × 4 Latin square designs under double-blind conditions. The subjects were tested before each drug (pre) and at 1h and 3h after the first dose on day 1. They were also tested before the first daily dose and at 1h and 3h after it on day 8.

Analysis of data A five way analysis of variance was calculated, the main sources of variance being subjects, drugs, occasions, times and days. Eight subjects, four drugs and four occasions allowed two Latin squares within the cells of which each subject was tested three times each on 2 days 7 days apart. Differences between drugs were obtained from the drugs × times and the drugs × days interactions. The following contrast analyses were computed: (a) placebo *vs* active drugs, (b) diazepam (5 mg) *vs* premazepam (5 mg + 10 mg) and (c) premazepam (5 mg) *vs* premazepam (10 mg). Only results which show the drugs to have a significantly different effect from placebo or from each other are reported. As *a priori* contrast analyses have been carried out in preference to *post hoc* testing, no indication of critical differences for individual points is given in the graphs.

Results

Single dose study

Self-ratings

Mood rating scale The subjects showed a significant change on factor 1 in the direction of *drowsiness* after the active drugs as compared with the placebo ($P<0.02$). They were most drowsy at 1h after each of the drugs. The greatest effect was shown by the combination dose of premazepam (25 mg) plus diazepam (10 mg) followed by premazepam (50 mg). For both of these drugs marked drowsiness persisted at 3h.

Bodily symptom scale The subjects felt *dizzy* after the active drugs as compared with the placebo ($P<0.02$). They reported feeling most dizzy after premazepam (50 mg) followed by the combination dose of premazepam (25 mg) plus diazepam (10 mg). Furthermore, *dizziness* was significantly greater with 50 mg premazepam than with the 25 mg dose ($P<0.01$). Each of the drugs showed the strongest effect at 1h. It was only after premazepam (50 mg) that *dizziness* persisted at 3h.

Physiological measures

Electroencephalogram The active drugs, when compared with the placebo condition, caused a significant decrease in the amount of activity in both the 4–7.5 Hz waveband (eyes open, $P<0.001$): eyes closed, $P<0.01$) and the 7.5–13.5 Hz waveband (eyes open, $P<0.05$) as well as a significant increase in the 13.5–26 Hz waveband (eyes open and eyes closed, $P<0.01$) (see Figure 1). Premazepam (25 mg and 50 mg) showed a greater effect than diazepam (10 mg) in the slower wavebands and a weaker effect in the fast waveband. The combination dose of premazepam (25 mg) plus diazepam (10 mg) caused a greater decrease in slow wave activity and a greater increase in fast wave activity than diazepam (10 mg).

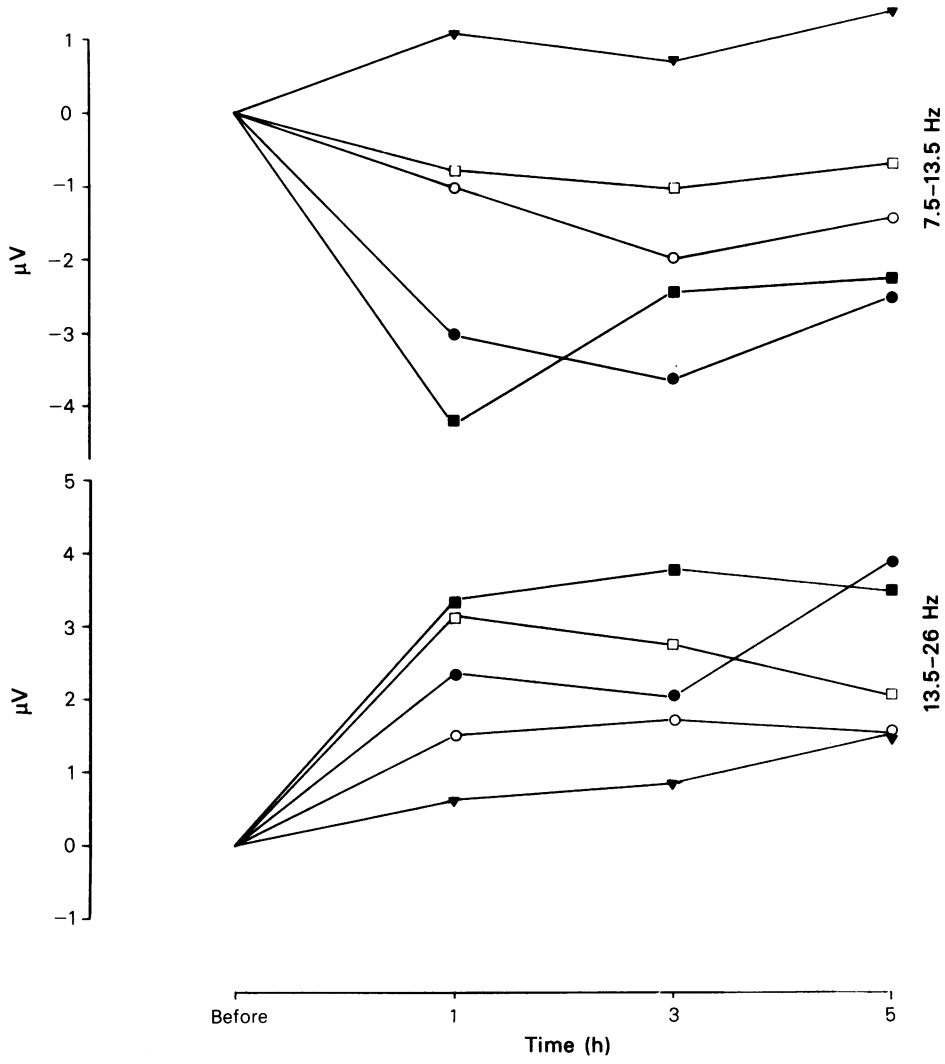

Figure 1 Mean scores in microvolts on the 7.5–13.5 Hz waveband and the 13.5–26 Hz waveband of the electroencephalogram under the eyes open condition after placebo (▼), premazepam 25 mg (○), premazepam 50 mg (●), diazepam 10 mg (□) and premazepam 25 mg + diazepam 10 mg (■). (single dose study).

Psychological measures

Tapping rate The combination dose of premazepam (25 mg) plus diazepam (10 mg) caused a significant reduction in the tapping rate as compared with the other active drugs ($P<0.05$).

Digit symbol substitution test The active drugs significantly decreased the number of symbols correctly substituted as compared with the placebo condition ($P<0.01$) (Figure 2). This effect persisted at 5h but was most marked for each of the drugs at 1h, particularly after the combination dose of premazepam (25 mg) plus diazepam (10 mg) and premazepam (50 mg).

Repeated dose study

Self ratings

Mood rating scale The comparison of diazepam (5 mg twice-daily) with premazepam (5 mg and 10 mg twice-daily) between the beginning of the week and the end of the week showed diazepam to cause significantly more drowsiness

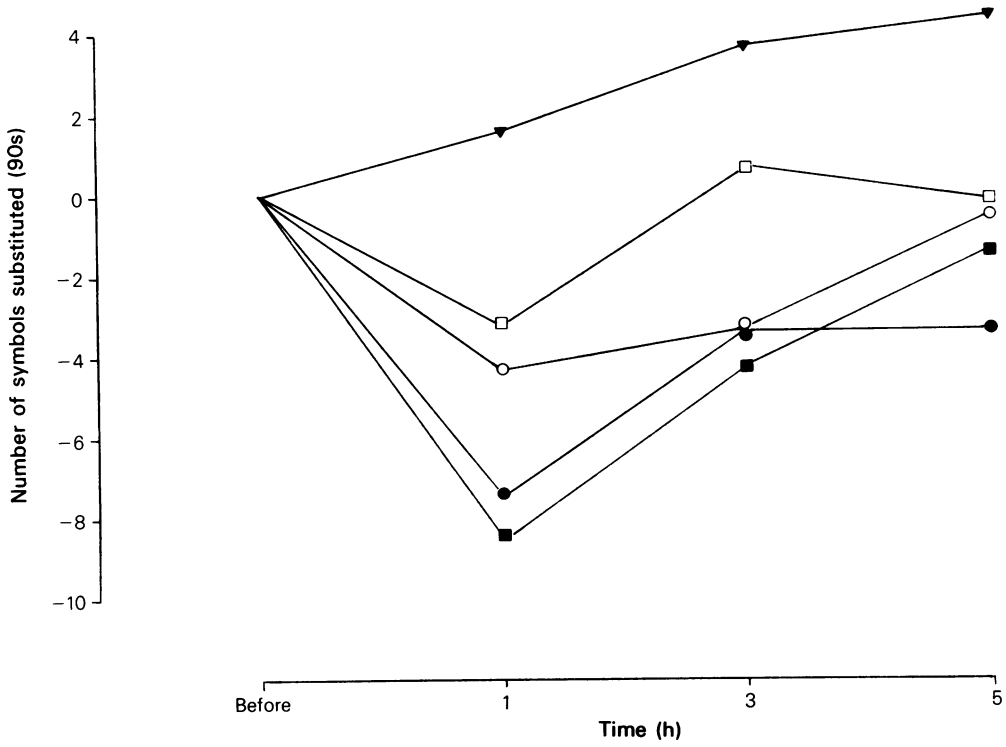

Figure 2 Mean number of symbols substituted in the digit symbol substitution test after placebo (▼), premazepam 25 mg (○), premazepam 50 mg (●), diazepam 10 mg (□) and premazepam 25 mg + diazepam 10 mg (■). (single dose study).

than both doses of premazepam on day 1 but not on day 8 ($P<0.05$).

Bodily symptom scale No significant differences were found between drugs on this measure.

Physiological measures

Electroencephalogram By the end of the week, the active drugs, when compared with the placebo condition, caused a significant decrease in the amount of activity in both the 4–7.5 Hz waveband (eyes open, $P<0.01$) and the 7.5–13.5 Hz waveband (eyes open, $P<0.01$) (see Figure 3). This effect was greater for the stronger dose of premazepam (10 mg) than for diazepam (5 mg) except under the eyes closed condition in the 7.5–13.5 Hz waveband. As shown in Figure 3, premazepam (5 mg and 10 mg) showed a weaker effect than diazepam (5 mg) in the 13.5–26 Hz waveband by the end of the week (eyes open, $P<0.001$; eyes closed, $P<0.05$).

Psychological measures

Tapping rate The effect of diazepam (5 mg) compared with premazepam (5 mg and 10 mg) for tapping differed significantly between day 1 and day 8 ($P<0.01$) showing that diazepam caused tapping to slow down at the beginning of the week but not at the end of the week.

Digit symbol substitution test The effect of diazepam (5 mg) compared with premazepam (5 mg and 10 mg) was found to be significantly different between day 1 and day 8 ($P<0.05$) indicating that diazepam had a greater effect, i.e. fewer symbols were substituted, than premazepam at the end of the week but not at the beginning of the week (see Figure 4).

Discussion

Diazepam showed a similar sedative action and

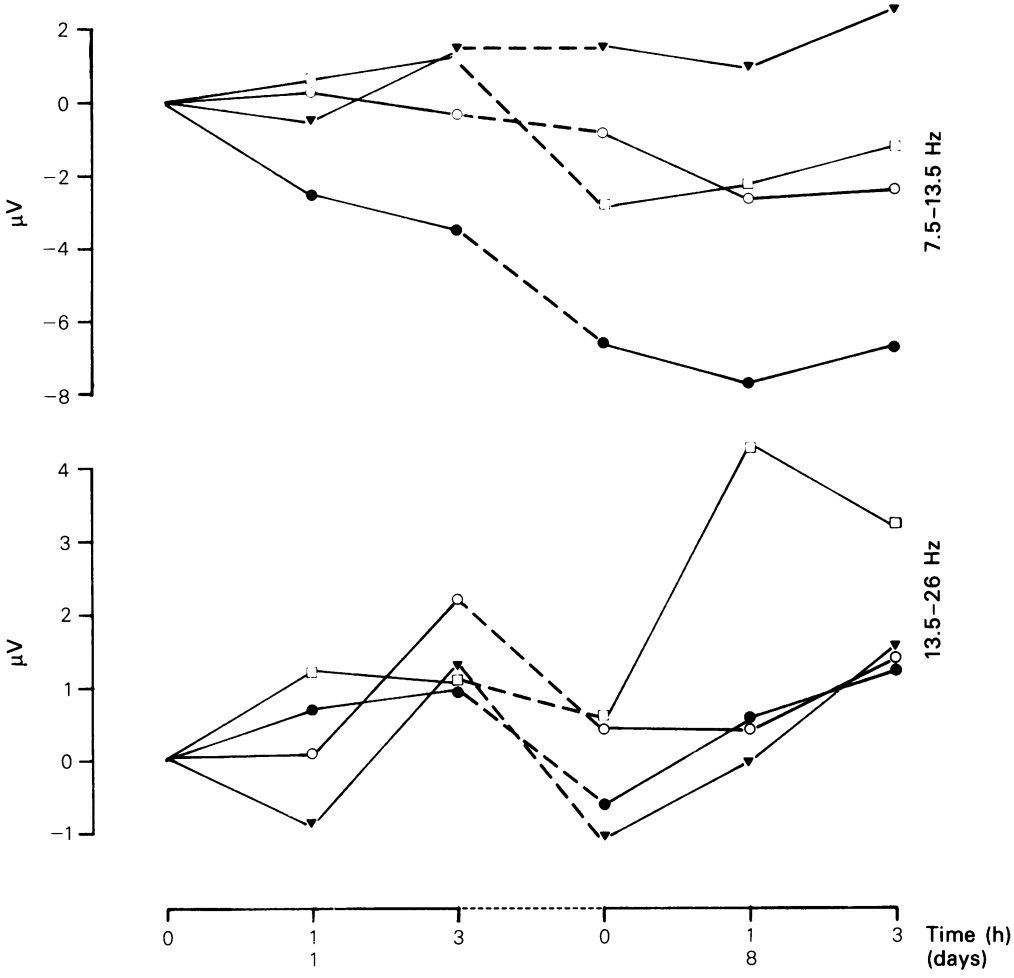

Figure 3 Mean scores in microvolts on the 7.5–13.5 Hz waveband of the electroencephalogram under the eyes open condition and the 13.5–26 Hz waveband under the eyes closed condition after placebo (▼), premazepam 5 mg (○), premazepam 10 mg (●) and diazepam 5 mg (□). (repeated dose study).

physiological changes to those found in previous studies (Bond & Lader, 1981, 1982; Bond *et al.*, 1983). Premazepam showed a rather different EEG profile from diazepam in the single dose study, with a greater decrease in the amount of slow wave activity and a smaller increase in fast wave activity. A similar EEG pattern was found for the larger dose of premazepam in the repeated dose study. However, the interpretation of these EEG differences must remain speculative. In the single dose study, the larger dose of premazepam resulted in more dizziness than diazepam and greater impairment on the digit symbol substitution test. However, the relatively lower doses of premazepam in the repeated dose study caused less sedation and less psychomotor impairment than diazepam. Furthermore it did not cause dizziness as in the single dose study.

The findings of the two studies indicate that a dose of 7.5 mg premazepam is roughly equivalent to 5 mg diazepam. The hypothesis that the combination dose of premazepam plus diazepam would reduce the sedative effects of diazepam was not supported by our findings. In fact, the evidence points to an additive effect rather than an antagonistic one. This underlines the problems involved in extrapolating from animal to human pharmacology. It also suggests that the dissociation between sedative and anxiolytic actions of tranquillisers, sought by many pharmaceutical companies, may prove elusive in practice.

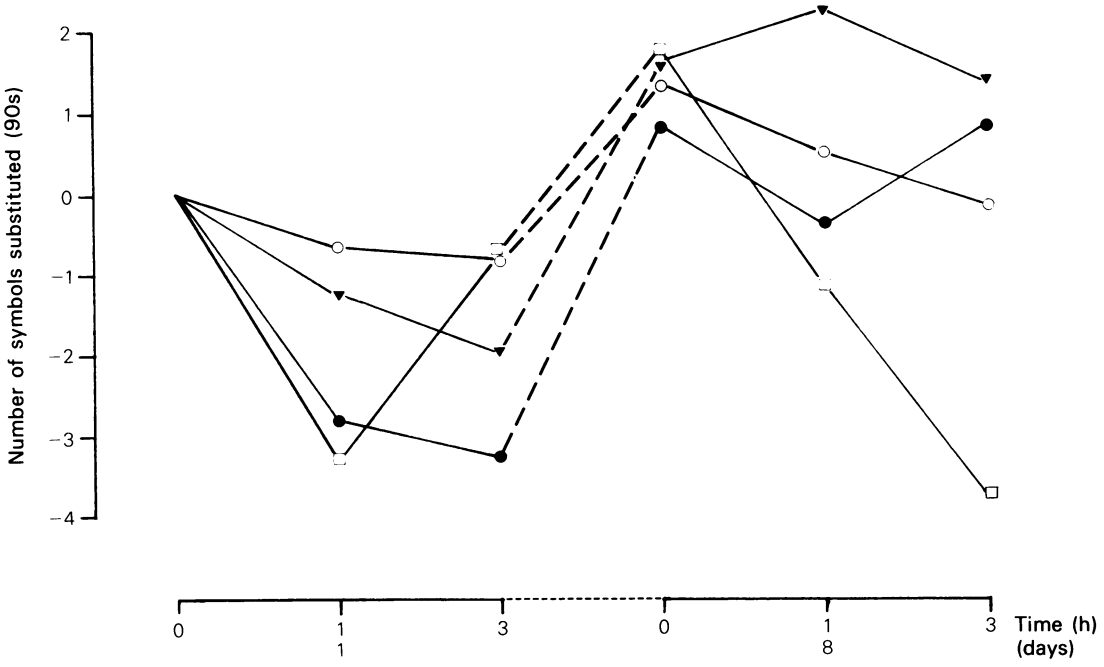

Figure 4 Mean number of symbols substituted in the digit symbol substitution test after placebo (▼), premazepam 5 mg (○), premazepam 10 mg (●) and diazepam 5 mg (□). (repeated dose study).

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