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EFFECTS ON PSYCHOLOGICAL PERFORMANCE OF THE BENZODIAZEPINE, LOPRAZOLAM, ALONE AND WITH ALCOHOL

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1 The effects of a new 1,4 benzodiazepine hypnotic, loprazolam (1.0 mg) and alcohol (0.7 g/kg body weight) were investigated over a 15 h period in eight healthy male medical students, in a placebo controlled balanced design.

2 Loprazolam when given alone impaired performance on a manual dexterity task, on a test of mental arithmetic, on a tracking task and it impaired memory as judged by the name and address memory test.

3 Given alone, alcohol impaired performance on the simple reaction time task and on the tracking task. Performance on the memory test and choice reaction time test actually improved.

4 No evidence was found suggesting a potentiation of effect when loprazolam and alcohol were given together. However,

(a) on the manual dexterity task the alcohol, having no effect on its own, alleviated the loprazolam-induced impairment.

(b) In the tracking task both alcohol and loprazolam impaired performance when given alone but not when given together.

(c) The memory test was impaired by loprazolam, improved by alcohol and the effect of the combination is the expected sum of the two effects. Similarly for the arithmetic task the effect of the combination of the alcohol and loprazolam effects is the expected sum of the independent effects.

5 The bulk of the evidence on the interaction suggests that alcohol mitigates the effects of loprazolam. In no sense could the drug be said to be having a sobering influence.

Keywords loprazolam alcohol psychological performance

Introduction

Benzodiazepines have been found to be a great advance over the barbiturates and other traditional drugs in the treatment of insomnia (Priest, 1978). In particular, they are much safer in overdose and they are very much less likely to produce physical dependence or convulsions and *delirium tremens* following withdrawal (Priest, 1978; Priest *et al.*, 1980).

When used to induce sleep the effects that sometimes prove troublesome include drowsiness and impaired psychomotor function on the following day and partial amnesia for events that occur while taking the medication. The first two of these problems are more liable to occur with those drugs that are long acting or have long acting metabolites (Bond & Lader, 1978).

The detrimental effects on cognitive and psychomotor performance induced by benzodiazepines are generally thought to be qualitatively similar to those produced by alcohol (Linnoila, 1973) and there is considerable evidence to suggest that these effects are enhanced by the ingestion of benzodiazepines and alcohol together (Linnoila & Mattila, 1973). The relevance of these interactions to the treatment of out-patients is well recognized.

There is now a wide choice of benzodiazepines available for use as hypnotics (Garrattini *et al.*, 1973; Priest *et al.*, 1979, 1980) but it is accepted that each has its imperfections (Priest *et al.*, 1980).

Many of the drugs currently available have active half-lives lasting 90 h or more (Drug & Therapeutics Bulletin, 1978) and there is considerable interest in new preparations with a shorter duration of action. One such drug is loprazolam (HR158 or RU31158; 6-(orthochlorophenyl)-1, 2-dihydro-2 (*N*-methyl-piperazine-1-yl) methylene-8-nitro-1H, 4H-imidazo [1,2-a] [1,4] benzodiazepine-1-one methanesulphonate; Dormonoct).

Johns *et al.* (1979) have demonstrated the potent

hypnotic activity of loprazolam compared to diazepam in the mouse and rat.

Hindmarch & Clyde (1980) confirmed the hypnotic activity of loprazolam in volunteers and recently Salkind & Silverstone (1983) and Boyd & Ankier (1983) have reported on the drug's hypnotic efficacy in patients with sleep problems.

In the present study loprazolam was tested for its effect on psychomotor performance, sleep and memory with the following expectations:

(a) The impairment of function demonstrated soon after ingestion of the drug would no longer be apparent the next morning.
(b) Impairment of function would be additive to that produced by alcohol.

Methods

Preparation

Capsules containing loprazolam (1.0 mg) or a matching placebo were used. For the experimental conditions demanding alcohol, vodka was administered, mixed with pure orange juice to make up a third of a litre of fluid. For the non-alcoholic conditions the capsules were given with a third of a litre of orange juice alone. The dose of alcohol was calculated at 0.7 g/kg body weight.

Subjects

Eight healthy male volunteers were accepted from a class of medical students. Although it was not made known to the subjects beforehand, the main criterion for selection was that volunteers should drink only in moderation, and this was defined as drinking in the average week not more than the equivalent of 15 pints of beer, or two bottles of sherry, or 3½ bottles of wine or one bottle of spirits (c.f. British Medical Journal, 1978). Other criteria were that they should not be taking drugs affecting the brain nor suffer from insomnia. The mean age of the subjects was 21.5 (s.d. 0.76), the mean height was 179.1 cm (s.d. 6.6.) and the mean weight was 70.5 kg (s.d. 7.5).

Tests used

Four of the tests employed were programmed for the Commodore PET computer with the instructions appearing on the visual display (programs available from I.C. McManus).

Tests (a) and (b) are conventional tests of psychomotor performance.

(a) *Simple reaction time (SRT)* A diagram of an open box was displayed on the computer screen. After a random time an asterisk appeared inside the box to which the subject had to respond by pressing the space key.

If the subject responded before or within 100 ms of the asterisk's appearance he was warned (automatically by a display) not to anticipate. The usual time taken for the complete testing was about 2 min. On each testing a subject produced 100 reaction times. The median reaction time was used as a measure of overall performance.

(b) *Choice reaction time (CRT)* Six open boxes were displayed on the computer screen. In pseudo-random sequence one of the boxes became solid and the subject had to respond by promptly pressing a key corresponding to the letter shown beneath the solid box. Subjects were informed at the beginning of the test which keys corresponded to which boxes. Reaction time and error rates were recorded for each of the 30 stimuli. If the subject responded before or within 100 ms of the stimuli he was warned not to anticipate. The usual time taken for the complete testing was about 2 min.

The third test is an adaptation of conventional paper and pencil tracking tests.

(c) *Tracking test (TRK)* A cursor was moved on a pseudo-random walk across the computer screen. The subject had four keys in use, two of which moved a second cursor to right or left at the same speed as the first cursor, and two of which moved the second cursor to left or right at double the speed of the first cursor. The subject's task was to keep the cursors aligned one above the other, and he was given feedback indicating the distance between the cursors during the task. The dependant variable was the absolute horizontal distance between the cursors and this was measured each time the cursor was moved and was analysed separately for each one-third of the experiment. The usual time taken for the complete testing was about one minute. The average overall deviation was used as a measure of performance.

The fourth test for which the computer was used was a calculation task for cognitive function.

(d) *Mental arithmetic (AR)* The subject was required to add or subtract a two-figure number from another two-figure number, both of which were displayed on the computer screen. The correct result was always a two-figure number. There were thirty tasks (15 additions and 15 subtractions) and the subjects received feedback on whether or not each response was correct. Response time, for addition and subtraction, and total number of errors were recorded. Most subjects completed the experiment in about 3 min.

Assessments of manual dexterity were used which did not involve the computer.

(e) *Manual dexterity* There were two tests:

(i) *Manual dexterity—nails (MADEN)* Using tweezers in their dominant hand, subjects were required to drop nails into a line of six holes in a board.

(ii) *Manual dexterity—Rivets (MADER)* Using their dominant hand, subjects were required to place rivets into a line of six holes in a board. The time taken for each task was recorded separately on a stop watch.

A test of memory was used that is based on traditional clinical practice.

(f) *Memory test (METE)* A name and address was read out to the subject who was asked to repeat each line as it was read. If an error was made, the subject was told the correct response and asked to repeat that line. At the end of the administration, the subject repeated the entire address and his answer was recorded. The whole procedure was repeated once if there were no errors, and twice, if errors were made in immediate recall. After 20 min he was asked to recall the name and address and his answer was recorded and scored. This test has been published elsewhere (Priest & Woolfson, 1978).

We wished to use simple measures that were not time consuming to assess the subjects' subjective responses in several dimensions relevant to experiences reported on benzodiasepines and we employed the visual analogue system described by Aitken (1969).

(g) *Visual analogue self-rating scales (VARS)* The subject had to rate his current feelings by marking the appropriate place on a 100 mm line for the four following dimensions

Left hand extreme	*Right hand extreme*
1. I am experiencing sensations of lethargy and lassitude.	Sensations of intense excitement and stimulation.
2. I am feeling very placid.	Experiencing intensely violent urges.
3. I am feeling in the depths of despair.	Complete cheerfulness.
4. I am feeling in full control of myself.	Completely lacking in inhibition.

The dimensions were designed to assess:

1. Stimulation, 'buzz', 'kick' or 'high'.
2. Aggression.
3. Affective mood changes.
4. Disinhibition.

(h) *St Mary's Hospital sleep questionnaire (SMH)* This is based on an earlier version used by one of the present authors (Priest & Rizvi, 1976). A standardised questionnaire on sleep is now available (Ellis *et al.*, 1981) which documents the subject's experience the previous night and also his relevant feeling the following morning with a high degree of reliability.

Study design All subjects were thoroughly informed about the protocol of the study and gave their written consent. They were required to abstain from drinking alcohol from the midnight previous to the trial until after the assessment the following day. On trial evenings, driving vehicles was not permitted and the subjects were taken home by taxi.

The investigation was a single dose cross-over study. There were two subjects in the laboratory at the same time. Double-blind secrecy was maintained on the contents of the capsule (placebo or loprazolam). In the absence of a true alcohol placebo it was ensured that when one subject received alcohol the other subject also received it.

For any subject pair, sessions 1 and 2 took place in the same week three days apart, and sessions 3 and 4 the following week.

Because performance on some of the tests shows a marked learning effect which could add to the variance of the results, all subjects were individually trained in these tests until they were past the very steep initial part of the learning curve.

During each session of the experiment itself baseline measurements were carried out at 20.00 h and the test substances given at 21.00 h. Tests (a) to (f) above were administered at 22.00 h, 23.00 h and 12.00 h the following day. Test (g) (VARS) was given at 23.00 h and again at 12.00 h the following day. Test (h) (Sleep assessment) was completed on waking the following morning.

Statistical analysis

Each of the eight subjects were tested on four successive *occasions* (pre-, 1 h, 2 h and 15 h) with each of four separate *conditions* (placebo, placebo + alcohol, loprazolam, loprazolam + alcohol) in four successive *sessions*. The order of presentation of the four conditions within the sessions was counter-balanced (see above) so that learning effects upon the tasks (i.e. session effects) could be discriminated from condition effects. The subjects were tested in pairs, and the particular pairing is the only between subject variable.

Table 1 summarises the basic analysis of variance design. The design involves repeated measures across subjects. Furthermore, condition and session are necessarily confounded and hence appear in the same

Table 1 Basic analysis of variance table

	d.f.	*Error term*	F *test d.f.*
Subjects	7	(d)	(7,54)
Pairs	3	(a)	(3, 4)
Subjects within pairs (a)	4	(d)	(4,54)
Condition	3	(b)	(3,18)
Session	3	(b)	(3,28)
Subjects × Session (b)	18	(d)	(18.54)
Occasion	3	(c)	(3,21)
Subject × Occasion (c)	21	(d)	(21,54)
Condition × Occasion	9	(d)	(9,54)
Session × Occasion	9	(d)	(9,54)
Subject × Condition × Occasion (d)	54	(d)	—
	127		

error stratum of the analysis. Variables omitted from the analysis are the order of alcohol presentation (first week or second), a between pair factor, and order of drug presentation (Mondays or Thursdays, i.e. sessions 1 and 3 or 2 and 4), which is a between subject, within pair factor. The design was balanced for these factors. Similarly the factor 'pair' was only included as a main effect, and its interactions with condition, session and occasion were omitted, in order to conserve error degrees of freedom. Subject effects and subject × factor effects were tested by using the necessarily conservative method of using the subject × condition × occasion mean square as an error term.

The condition, occasion and session effects shown in Table 1 were further partitioned. The conditions effect was partitioned into loprazolam treatment, alcohol treatment, and loprazolam by alcohol interaction contrasts. It should be noted, therefore, that the loprazolam effect refers to the whole of a particular session and, therefore, includes the pre-treatment measurement and the 15 h post-treatment measurement. The occasions effect was partitioned into three contrasts which are shown in Table 2. These contrasts were used on the assumption that drug-levels would rise to a maximum in 1–2 h and be almost minimal by 15 h post-administration. Hence, contrast T1 compares 1 and 2 h tests with pre- and 15 h tests and may be called a 'Medication' effect (Medication referring to loprazolam, alcohol, both or neither), the assumption being that the baseline performance (pre- and 15 h) is best compared with performance of 1 and 2 h after administration in order to produce maximum sensitivity. Contrast T2 compares only the pre-treatment assessment with the 15 h assessment and hence may be regarded as assessing a 'hang-over effect'. This contrast, therefore, ignores all of the acute effects of the medication and considers only the longer term effect of the medication. Finally, for completeness, the third contrast, T3, compares 1 and 2 h assessments; since concentration of medication may still be changing over this period, the contrast may loosely be called 'kinetic effect'. It must be noted from the nature of this analysis that if, say, only T2 is significant without any significant condition effect, this probably reflects a circadian rhythm in performance, the important point being that the T1 contrast alone includes the observations where only a placebo had been administered. If just a condition effect is significant, then this probably represents a true effect of the treatment, but could conceivably indicate a 'placebo' response on the part of the subject. A true effect of a condition will be indicated by the existence of a condition by occasion interaction. Thus, if alcohol is truly affecting performance, it would be expected that there would be a significant T1 × alcohol interaction. The session effect was partitioned into (a) a linear trend and (b) a deviation from

Table 2 The three orthogonal contrasts used for analysing the occasion effects

	Pre- 20.00 h	*1 h post 22.00 h*	*2 h post 23.00 h*	*15 h post 12.00 h*	
T1	−1	1	1	−1	'Medication effect'
Contrast T2	1	0	0	−1	'Hangover effect'
T3	0	1	−1	0	'Kinetic effect'

Table 3 Complete analysis of variance design

	d.f.	*Error term*	F *test d.f.*
Subjects	7	(d)	(7,54)
Pairs	3	(a)	(3, 4)
Subjects within pairs (a)	4	(d)	(4,54)
Alcohol	1	(b)	(1,18)
Loprazolam	1	(b)	(1,18)
Alcohol × Loprazolam	1	(b)	(1,18)
Session—linear	1	(b)	(1,18)
Session—non linear	2	(b)	(2,18)
Subjects × Session (b)	18	(d)	(18,54)
'Medication'	1	(c)	(1,21)
'Hangover'	1	(c)	(1,21)
'Kinetic'	1	(c)	(1,21)
Subjects × Occasion (c)	21	(d)	(21,54)
Alcohol × 'Medication'	1	(d)	(1,54)
Alcohol × 'Hangover'	1	(d)	(1,54)
Alcohol × 'Kinetic'	1	(d)	(1,54)
Loprazolam × 'Medication'	1	(d)	(1,54)
Loprazolam × 'Hangover'	1	(d)	(1,54)
Loprazolam × 'Kinetic'	1	(d)	(1,54)
Alcohol × Loprazolam × 'Medication'	1	(d)	(1,54)
Alcohol × Loprazolam × 'Hangover'	1	(d)	(1,54)
Alcohol × Loprazolam × 'Kinetic'	1	(d)	(1,54)
Session × Occasion	9	(d)	(9,54)
Subject × Condition × Occasion (d)	54	—	—
	127		

a linear trend (with 2 degrees of freedom). The complete analysis of variance design is summarised in Table 3.

In view of the large number of possible results and the large number of dependent variables to be described, only a tabular summary of significance levels will be given, along with a graph for some of the dependent variables showing the relation to the condition and the occasion of testing.

Results

Simple reaction time

There was a significant tendency towards longer reaction times during 'medication' periods. This is reflected in a non-significant trend towards longer reaction times in the loprazolam alone condition, but the only statistically significant trend is of alcohol upon reaction time. The picture is, therefore, rather confused.

Choice reaction time

The mean choice reaction time showed a linear trend across sessions, from a mean of 510 ms on the first session to 443 ms on the last. The different conditions had little effect upon the mean time, although there was a significant tendency for alcohol to decrease reaction times and an almost significant tendency for loprazolam to lengthen reaction times. Errors on the choice reaction task showed little systematic relation to any of the variables (Table 4). However, the number of errors was relatively low (Mean of 1.02 per occasion) and thus precludes any reasonable analysis.

Tracking task

Overall performance on the tracking task showed a large improvement in performance across sessions, the performance apparently reaching a plateau by the third session. The analysis shows a significant effect of the alcohol × loprazolam interaction and an almost significant T1 × alcohol × loprazolam interaction. The interpretation of this combination of results seems fairly clear; both loprazolam and alcohol on their own significantly impair performance 1 and 2 h after ingestion; however, the combination effect of alcohol and loprazolam is less than would be expected on the basis of independent additive effects of the two substances (Figure 1).

Arithmetic test

This test produced three separate dependent vari-

Table 4 Significance levels of nine dependent variables in analysis of variance

	Simple reaction time	*Choice reaction time*		*Tracking task*	*Arithmetic task*			*Manual dexterity tests*	
	Median	*Mean*	*Errors*	*Average*	*Addition Mean*	*Subtraction Mean*	*Errors*	*Nails*	*Memory*
Pairs	0	0	0	0	0	0	0	0	0
Subjects	***	***	***	+	***	***	**	***	*
Session—linear	0	***	0	***	***	***	0	**	0
Session—non-linear	0	0	0	*	0	0	0	0	0
Alcohol	0	0	0	0	0	0	0	**	*
Loprazolam	0	0	0	0	**	*	0	0	***
Alcohol × Loprazolam	0	0	0	*	+	0	0	0	0
'Medication'	*	0	0	0	**	*	0	0	**
'Hangover'	0	0	0	0	+	0	0	0	*
'Kinetic'	0	0	0	0	*	+	0	0	0
Medication × Alcohol	*	*	0	0	*	0	0	0	0
Hangover × Alcohol	0	0	0	0	0	*	0	0	0
Kinetic × Alcohol	0	0	*	0	*	0	+	0	0
Medication × Loprazolam	0	+	*	0	*	**	0	**	**
Hangover × Loprazolam	0	0	0	0	0	0	0	0	0
Kinetic × Loprazolam	0	0	0	0	0	0	0	0	0
Medication × Loprazolam × Alcohol	0	0	0	+	0	0	0	**	0
Hangover × Loprazolam × Alcohol	0	0	0	0	0	0	0	0	0
Kinetic × Loprazolam × Alcohol	0	0	0	0	0	0	0	0	0

0 = NS, + = $P < 0.1$, * = $P < 0.05$, ** = $P < 0.01$, *** = $P < 0.001$.

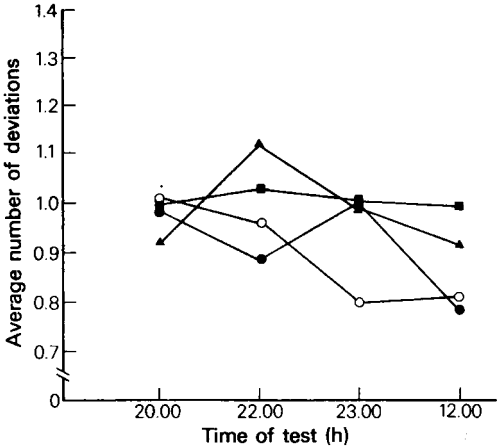

Figure 1 Tracking test (average). ■ loprazolam (1 mg) alone, ▲ alcohol (0.7 g/kg) alone, ● loprazolam (1 mg) + alcohol (0.7 g kg) and O placebo.

ables, the mean response times on addition and subtraction and the overall error rate. The mean response times both showed significant differences across sessions (from 4.29 to 3.49 s for addition and 5.09 to 3.95 s for subtraction on the first and last sessions, respectively). Both addition and subtraction showed significant effects for contrast T1 and for loprazolam treatment and for the loprazolam × Ti interaction.

Addition also showed a trend towards a significant alcohol × loprazolam interaction, although there was no suggestion of this for subtraction. The loprazolam treatment, therefore, appears to impair speed of performance upon both tasks (Figures 2 and 3). The error rate showed no meaningful pattern of results although as with the choice reaction task the rate was very low (1.46 errors per occasion).

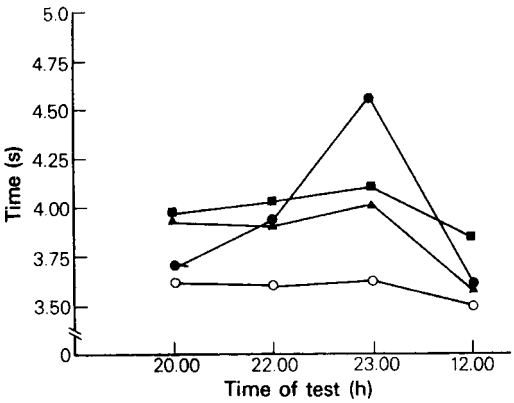

Figure 2 Arithmetic (additions) test. ■ loprazolam (1 mg) alone, ▲ alcohol (0.7 g/kg), alone, ● loprazolam (1 mg) + alcohol (0.7 g/kg) and O placebo.

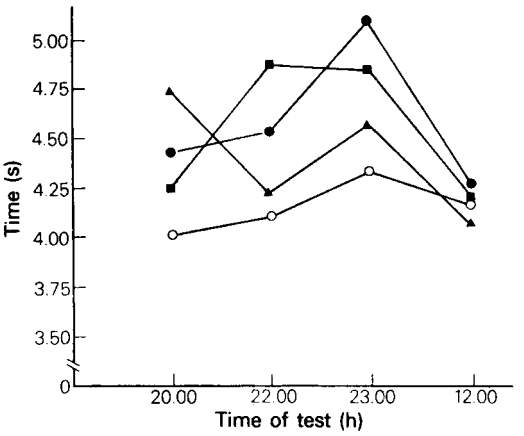

Figure 3 Arithmetic (subtractions) test. ■ loprazolam (1 mg) alone, ▲ alcohol (0.7 g/kg) alone, ● loprazolam (1 mg) + alcohol (0.7 g kg), and O placebo.

Manual dexterity

The two manual dexterity tasks with nails and rivets, showed different patterns of results and will be considered separately. On the nails task, there was a significant linear trend across sessions (mean time = 25.8 s and 21.2 s on the first and last session respectively). There were also significant effects of 'alcohol' treatment, T1 × loprazolam interaction and a T1 × alcohol × loprazolam interaction. Figure 4 suggests

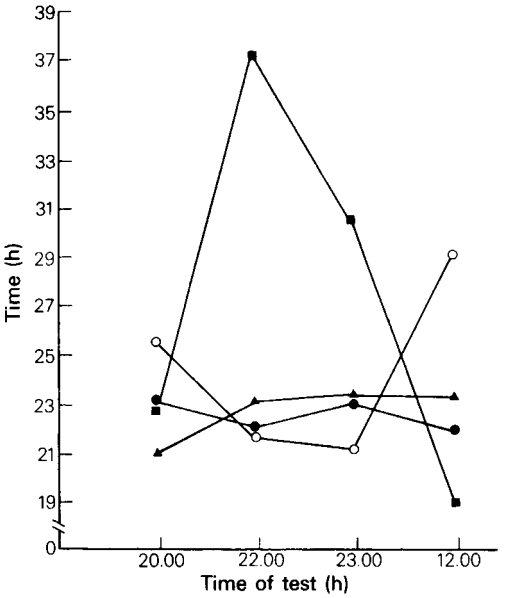

Figure 4 Manual dexterity (nails) test. ■ loprazolam (1 mg) alone, ▲ alcohol (0.7 g kg), alone, ● loprazolam (1 mg) + alcohol (0.7 g/kg) and O placebo.

that loprazolam, on its own, significantly impairs performance but that this impairment is alleviated by the presence of alcohol.

On the rivets task, there was a linear trend across sessions (mean time = 17.1 s on the first session and 13.5 s on the last session). There was also a significant T3 × alcohol × loprazolam interaction, which did not have a clear interpretation.

It is not clear why the two manual dexterity tasks should show such a different pattern of results.

Memory test

The memory test showed no trend across sessions.

There were significant effects of contrast T1 and T2 of 'alcohol treatment' and 'loprazolam treatment' and a T1 × loprazolam interaction. Figure 5 shows that loprazolam significantly impairs memory. This impairment is not statistically significant 15 h after administration of the drug. Alcohol improves memory performance whether or not the subject is given loprazolam.

Discussion

For the purpose of this study, we wished to select volunteers who did not habitually consume excessive quantities of alcohol. However, it is difficult to know how to decide exactly what level should be regarded as excessive. Liver damage in men is caused, possibly, by a daily intake of 60 g alcohol (3½ pints of beer) and those taking more than 170 g run a high risk of cirrhosis (British Medical Journal, 1978). Various recommendations are cited by the Office of Health Economics (1981), including two, three, four or five pints of beer a day (or their equivalents). The cut-off point used for the selection of the volunteers in this study (15 pints a week) comes closest to the lowest of these limits. The mean daily intake of male drinkers over 20 years of age in England and Wales is the equivalent of about 10 pints a week. The dose of alcohol chosen for experimental use in this study was at a level, such, that effects were likely to be demonstrable in the laboratory (Taeuber *et al.*, 1979) but that intoxication would not be so severe as to prevent the subjects being able to look after themselves after having been returned to their individual residences.

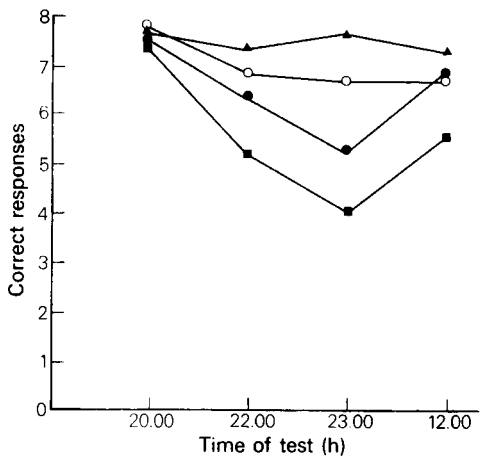

Figure 5 Memory test. ■ loprazolam (1 mg) alone, ▲ alcohol (0.7 g/kg) alone, ● loprazolam (1 mg) + alcohol (0.7 g/kg), and O placebo.

Turning to the results of our investigation, we found evidence of only very small effects of alcohol and loprazolam upon the relatively easy tasks of simple reaction time and choice reaction time. Both loprazolam and alcohol had more pronounced effects upon the other more complex tasks. Loprazolam alone impaired performance on a tracking task, on an arithmetic task, on the nails manual dexterity task and on the memory task; in no case was there evidence for a significant hangover effect of loprazolam 15 h after administration. The effect upon the memory task was particularly striking, given the relatively low error rate in the control condition on a rather simple task. Alcohol on its own impaired performance upon the tracking task and improved performance on the memory task.

There are many points of similarity in the commonly observed effects of benzodiazepines and alcohol (Priest, 1982). Both relieve anxiety in small doses. With further increases in dose, they produce sleep, followed by coma. Intoxication doses in the ambulant subject produce ataxia, dysarthria, diplopia and nystagmus. Physical dependence to either carries with it a liability to withdrawal syndromes of convulsions and delirium. It is, of course, partly because of these similarities in action that one wishes to look for evidence of interaction. Yet, in the present study, we found no evidence for potentiation.

The interactions that we did find follow several different patterns and must be considered separately.

(a) On the nail test of manual dexterity, the loprazolam alone impaired performance but the addition of alcohol 'removed' the impairment: thus, the alcohol is apparently alleviating the loprazolam-induced deficit.

(b) In the tracking task, both alcohol and loprazolam separately impair performance; however, when given together, performance is relatively improved and thus, one seems to be alleviating the impairment of the other.

(c) In the case of the memory task, the loprazolam impairs performance, the alcohol improves it and

there is no evidence of any interaction at all, the effect of both being the sum of the two components. Similarly, for the mental arithmetic tests, there was evidence of independent effects of alcohol and loprazolam but of no interaction between the two.

The bulk of the evidence on the loprazolam–alcohol interaction suggests, therefore, that in general, alcohol is alleviating the disadvantage of the drug, rather than *vice versa*. It would certainly be quite misleading to suggest that the overall effect of loprazolam is a sobering one.

English *et al.* (1982) also found effects on psychomotor performance of both benzodiazepines and alcohol, but concluded that alcohol did not appear to potentiate the effect of those benzodiazepines (nitrazepam and temazepam). However, they used smaller doses of alcohol, ranging from 0.1 mg to 0.4 g/kg. Looking at the 'morning after' effect, Hindmarch & Gudgeon (1982) failed to show any statistically significant impairment of performance in tests of psychomotor ability the morning following 3 nights administration of either 15 g flurazepam with alcohol (0.5 ml/kg) or 1 mg loprazolam with alcohol. They did find subjective responses, in that flurazepam with alcohol produced a greater impairment of subjects' ratings of early morning behaviour than either loprazolam or placebo taken with alcohol.

The presence of the interaction found in (a) and (b) above between a benzodiazepine and alcohol suggests that they might be acting through some common central neuro-transmitter system with the two actions competing in some way. In this context it is of interest that a recent report suggests that prenatal exposure to alcohol in rats leads to subsequent tolerance to both benzodiazepines and barbiturates (Abel *et al.*, 1981).

Nevertheless, the nature of such a common central neuro-transmitter system remains speculative. There is evidence for the existence of more than one benzodiazepine receptor (Braestrup & Neilsen, 1980a,b). However, long-term treatment of rodents with alcohol seems to induce either no change (Karobath *et al.*, 1980) or very little (Freund, 1980) in the number of receptors in the brain.

Although amnesia is recognised as a side-effect of administration of benzodiazepines (Priest, 1982) the accounts tend to be clinical and anecdotal and it is unusual for this action to be reported systematically in a laboratory study. The Name and Address Memory Test was designed for assessing the major impairments of memory found in psychiatric patients with organic brain disease. It is gratifying to find that it proved to be sensitive to the degree of amnesia produced in the conditions of this experiment, as shown by the results displayed in Figure 5. We would recommend more widespread use of a standardised memory test when reporting the characteristics of a new benzodiazepine.

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