

Effects of Ethanol and Temazepam on Performance in Memory and Psychomotor Tasks: a Dose-Response Comparison

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In order to compare the effects of ethanol and a benzodiazepine on psychomotor performance and memory, 15 subjects (nine male, six female) aged 20–27 years took part in a five-period crossover study in which they received by mouth in randomised order: (1) ethanol 0.88 g/kg, maximum 66 g for males, 55 g for females; (2) ethanol, 0.75 of condition 1; (3) temazepam 20 mg; (4) temazepam 15 mg; (5) placebo. Both drugs led to significant subjective drunkenness and drowsiness; drunkenness was more marked for ethanol, drowsiness for temazepam. Psychomotor slowing in Digit/Symbol substitution tasks was similar for the two drugs. In the Four-Choice Reaction-Time Task, subjects on ethanol tended to respond faster during the sections of the task where a repetitive sequence of stimuli was given, while those on temazepam slowed down. In the sections with random stimulus sequences, both drugs led to slowing. Ethanol, but not temazepam, led to increased errors in this task. The effect of ethanol on long-term memory in the Buschke selective reminding task was very marked. The trend for temazepam was in the same direction, but not statistically significant. All performance effects were dose-dependent, except the speeding on the Four-Choice task, where the two doses of ethanol had similar effects. These results show that dissociations occur between ethanol and temazepam, ethanol producing more errors at a similar degree of slowing of performance. The effects of ethanol on memory are particularly marked relative to its sedative effect. © 1998 John Wiley & Sons, Ltd.

Hum. Psychopharmacol. Clin. Exp. 13: 285–291, 1998.

KEY WORDS — ethanol; temazepam; psychomotor performance; memory; driving-related skills; automatic processing; control processing

INTRODUCTION

Many drugs affect the degree of arousal of the CNS, either acting as stimulants or sedatives. Sedation (or more generally CNS depression) is of particular concern, in view of the link with accidents, whether on the roads, at home or at work.

Drugs with such properties form a very varied group. In some cases the CNS depression is an intended action of the drug (e.g. hypnotics, anaesthetics); in other cases it is an unwanted side-effect (many antidepressants and older antihistamines); sometimes the relationship between the principal pharmacological action and CNS depression is unclear (antipsychotic drugs, anticonvulsants and

ethanol). The primary pharmacological actions of sedative drugs are also diverse, including a variety of specific receptor interactions, as well as more general actions on neuronal membranes.

In view of this diversity, it might be expected that the behavioural and functional effects of such drugs would be equally distinct. However, the similarities are much more marked than any differences. Although some reports indicate selective actions (e.g. benzodiazepines on memory, see e.g. Curran and Birch, 1991), all such drugs slow reaction times and impair various aspects of cognitive function, including attention, memory and problem solving (Hindmarch, 1980; Curran *et al.*, 1988; Millar *et al.*, 1995).

Selective actions of ethanol are of particular interest in view of the involvement of that drug in

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accidents. A recent study (Newman *et al.*, 1997) suggested that ethanol had a disproportionate effect on responses requiring a shift of attention as compared to overall response times in a serial reaction time task. This finding may relate in particular to potential accident situations, where unexpected events occur in a context of automatic performance with low attentional demands. This study used ethanol only, so issues of drug specificity were not addressed.

The issue of dose-response is of great importance in such comparisons, in that the effects of drugs on many functions is not linearly related to dose. Thus single-dose comparisons may be misleading unless a clear double dissociation can be obtained. This makes interpretation of a number of the studies in the literature concerning selective memory effects of benzodiazepines difficult (see e.g. Curran *et al.*, 1993).

The present study therefore compared the effects of low and moderate doses of alcohol and temazepam on several measures likely to distinguish between the two drugs, including a memory task; the serial reaction time task used by Newman *et al.*; and some well-established measures of performance known to be sensitive to the effects of both classes of drug.

METHODOLOGY

Design

The study used a randomised, double-blind five-period design. Subjects took part in five sessions, at least 2 days apart, in which they received by mouth either (1) ethanol (calculated to produce peak blood ethanol concentrations around the UK legal limit for driving (80 mg/100 ml); (2) ethanol at 0.75 the dose used in (1); (3) temazepam, 20 mg; (4) temazepam 15 mg; or (5) placebo. The order of administration was randomised in blocks of five subjects. Performance testing and subjective ratings were carried out before treatment, and at intervals over the next 2 h.

Subjects

Fifteen subjects, nine male and six female, aged between 20 and 27 years (mean 22.2), and weighing between 49 and 90 kg (mean 67) took part in the study. All were healthy as assessed at initial screening, and all were light to moderate social drinkers. Subjects gave written informed consent to

participate in the study, which was approved by the Ethics Committee of the Lothian Health Board.

Assessments

The following tests were administered:

Four-Choice Reaction-Time Task (Wilkinson and Houghton, 1975; Tiplady, 1991). An array of four squares on a monitor screen corresponded to four buttons on a response box. The squares 'lit up' in sequence, and the subject responded by pressing the appropriate button as quickly as possible. Some of the time the sequence of stimuli was random, at other times a particular sequence of four lights was repeated 8–12 times. The mean response times for three blocks of repetitive and random sequences, and the times for the responses immediately following the transition from repetitive to random, were recorded, as well as the corresponding error scores.

Buschke Selective Reminding Task (Buschke and Fuld, 1974). The experimenter read a list of 15 words to the subject, who then recalled as many words as possible in any order. The experimenter then read out those words not recalled on the first occasion, and the subject again attempted to recall the entire list. This procedure was repeated six times. Measures of recall from long- and short-term memory, as well as forgetting from long-term memory, were obtained.

Digit-Symbol Substitution and Symbol-Digit Substitution. These were performed as previously described (Tiplady, 1991; Armstrong *et al.*, 1991).

Subjective assessments. These were made using visual analogue scales.

The order of administration of the test measures was randomised between subjects. The same order was used for all five sessions for any particular subject.

Equipment

The Visual Analogue Scales were presented on an Apple MessagePad 130 (a pen-based device). The Four-Choice Reaction Test and Symbol-Digit Substitution used the BBC Master microcomputer with a custom response box. Digit-Symbol Substitution was presented using pencil and paper.

Procedures

Each subject first took part in a familiarisation session in which the test procedures were demonstrated and all tests were carried out at least twice.

Subjects then took part in five sessions, all at the same time of day. They were instructed not to use tobacco during test days from 2 h before the beginning of the test session until the end of all procedures, and to take no alcohol from 24 h before the start of the test session until the end of the day. They were instructed to drink a maximum of one cup of tea or coffee at breakfast (to be the same on each test day), and thereafter to abstain from caffeine-containing drinks until the completion of the session. No food was to be consumed for at least 4 h before the beginning of the session.

All test measures, except the Selective Reminding Task, were performed before ethanol administration (baseline). Subjects then received a capsule and a drink. The capsule contained 20 or 15 mg of temazepam, or placebo (lactose). The drink consisted of vodka or water made up to 500 ml with orange concentrate and water. The higher dose of ethanol was 0.88 g/kg, up to a maximum of 66 g total for males, 55 g for females. The lower dose was 75 per cent of the higher dose. To ensure blind

administration, subjects sucked a Tyrozet lozenge (containing the local anaesthetic benzocaine) before consuming the drink, which was sprayed with a peppermint breath freshener. The drink was consumed within 10 min.

The test battery was then administered at 45 and 90 min post-drug, these times representing the mid-points of the testing periods.

Statistical analysis

The mean of the two post-drug values for each test measurement were analysed using Analysis of Variance (PROC GLM in SAS). The overall treatment effect was first examined. If this showed statistical significance the pairwise differences were examined.

RESULTS

Data from the test battery are shown in Table 1. The time-course of the effects of ethanol are illustrated in Figure 1, and a comparison of the effects of the larger doses of the two drugs on subjective and psychomotor measures are shown in Figure 2. Details of the dose-response relationships for

Table 1. Effects of ethanol on objective and subjective measures of CNS function. Mean effects are shown together with the standard error (S.E.)

Test measure	PLA	A1	A2	T1	T2	S.E.
<i>Four-Choice Reaction Test</i>						
Random RT (ms)	309	316	332**	326	339**	5.73
Repetitive RT (ms)	222	204	205	243	263**	8.80
Slowing on repetitive/random transition (ms)	91	107	130	107	109	16.5
No. of errors, random sequence	3.6	5.9*	8.7**	3.8	4.3	0.76
No. of errors, fixed sequence	1.0	1.4	2.4**	1.1	1.2	0.30
No. of errors, fixed/random transition	0.85	1.1	1.4	0.93	0.58	0.19
<i>Buschke Memory Task</i>						
Short-term recall (%)	16.9	31.4	32.6	21.3	27.6	4.89
Long-term recall (/15)	9.7	7.6*	5.4**	9.1	8.4	0.60
Long-term forgetting	1.65	2.58	4.0**	1.51	2.58	0.55
<i>Digit-Symbol Substitution</i>						
No. in 90 s	75.6	71.9*	65.2**	71.4*	65.3**	1.25
<i>Symbol-Digit Substitution</i>						
No. in 90 s	61.7	56.7**	53.8**	57.1**	55.1**	0.76
<i>Visual Analogue Scales</i>						
Alert-Drowsy (mm)	33.1	44.6	54.4**	56.8**	60.4**	4.81
Drunk-Sober (mm)	85.4	41.7**	31.5**	67.0*	63.6**	4.12

RT = response time. * $p < 0.05$, ** $p < 0.01$ compared to placebo.

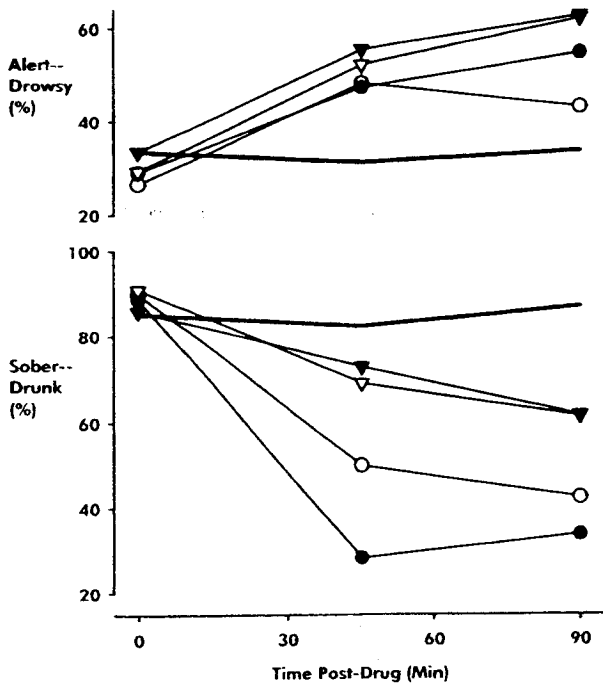


Figure 1. Time course of subjective effects assessed by Visual Analogue Scales. Units are the percentage of the total scale length. Solid line: placebo; circles: ethanol; triangles: temazepam; open markers: low-dose; closed markers: high-dose

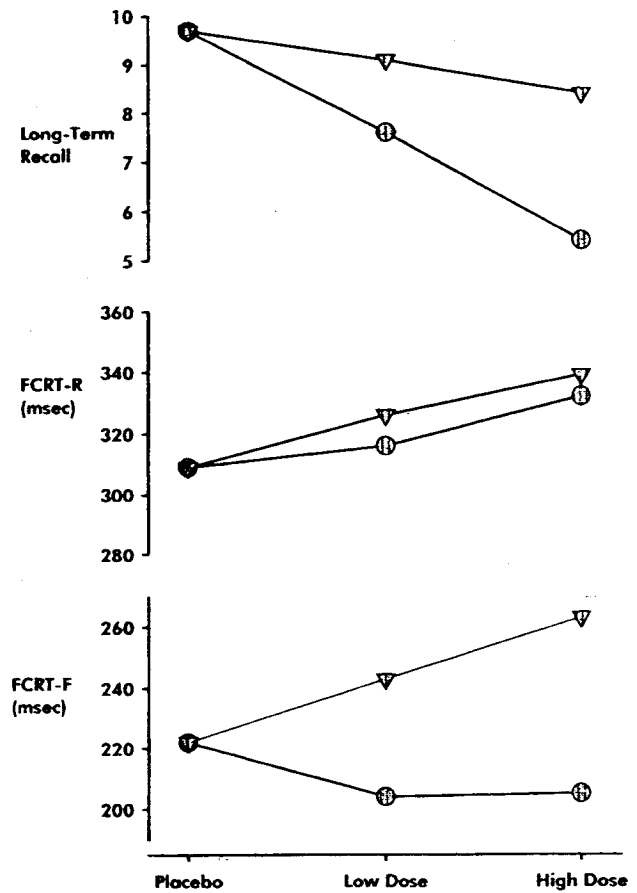


Figure 3. Dose-response comparisons for Buschke Long-Term Recall and for random (FCRT-R) and fixed (FCRT-F) sequence response times for the Four-Choice Reaction-Time test. Circles: ethanol; triangles: temazepam. The low and high doses are in the approximate ratio of $1 : \sqrt{2}$, so a linear plot indicates a response proportional to dose squared (cf. Armstrong *et al.*, 1995)

Selective Reminding and Four-Choice Reaction-Time Tasks are shown in Figure 3.

It can be seen that most test measures are affected by the high dose of ethanol, while the effects of temazepam are mainly seen in the reaction time and subjective measures. On the

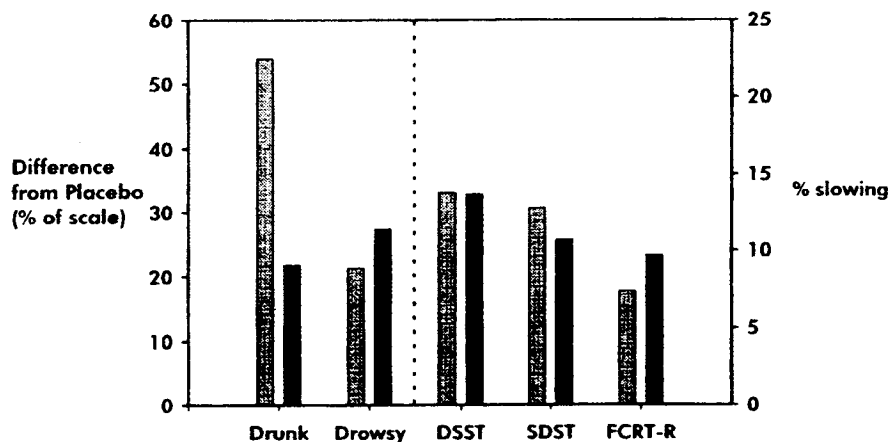


Figure 2. Comparison of the effects of high dose ethanol and temazepam compared to placebo. Drunkenness and drowsiness were expressed in terms of the percentage of the total Visual Analogue Scale length. Digit-Symbol Substitution (DSST), Symbol-Digit Substitution (SDST) and Four-Choice Reaction-time — Random Sequences (FCRT-R) were expressed as the percentage slowing compared to placebo. Grey columns: ethanol; black columns: temazepam

Four-Choice Reaction-Time Task, higher-dose temazepam slowed responding in both the random and repetitive sequences (9.7 and 18 per cent respectively, both $p < 0.01$). By contrast, higher-dose ethanol slowed the responses to the random sequences (7.4 per cent, $p < 0.01$), but the repetitive sequences tended to speed up (7.7 per cent, n.s.). While the difference between ethanol and placebo for fixed sequences was not significant, that between ethanol and higher-dose temazepam was ($p < 0.01$). The slowing of the first random response after a repetitive sequence was increased by 43 per cent for higher-dose ethanol and by 20 per cent for higher-dose temazepam, but neither of these differed significantly from placebo. Errors during both fixed and random sequences were significantly increased by ethanol, but not by temazepam. Digit-Symbol and Symbol-Digit Substitution were significantly slowed by all active treatments. Memory performance was also impaired by ethanol but not by temazepam, the largest effect being the reduction in recall from long-term memory by higher-dose ethanol ($p < 0.01$). Subjective drunkenness and drowsiness were observed for both drugs. While temazepam was associated with a slightly more drowsiness than ethanol, the latter produced a markedly greater degree of drunkenness.

DISCUSSION

For a dose-response comparison to work effectively, there must be good match between the doses of the two drugs used. The data in Figure 2, illustrating subjective data together with the three simple speeded measures used in the study, indicate that this is the case here. Very similar degrees of slowing are produced by the higher doses of the two drugs — 13.8, 12.8 and 7.4 per cent for Digit-Symbol, Symbol-Digit and Four-Choice Random Reaction Time, respectively, for ethanol, and 13.7, 10.7 and 9.7 per cent for temazepam. This indicates that similar reductions in information processing capacity have been produced. For subjective drunkenness and drowsiness, each drug produced a greater degree of its more characteristic action. Thus the doses chosen appear to have been appropriate.

Psychomotor performance

The results from the fixed-random transition in the Four-Choice task showed a marked increase in the

slowing with ethanol, which was rather greater than that for temazepam. This difference did not, however, reach statistical significance. Much more striking is the contrast between the two drugs on the fixed and random sequences. While the results for the random sequences are similar, both drugs showing significant slowing, this is not the case for the fixed sequence reactions, nor for error scores. Subjects slow down significantly on the fixed sequences with temazepam, but tend to speed up with ethanol. Now while speed of responding during the random sequences is limited by information processing capacity, this is not the case for the fixed sequences. Speed is limited rather by the knowledge that in due course the fixed sequence will end, and become random again, that is by the subject's judgement.

The nature of the observed change with ethanol fits in well with the view of ethanol action described by Steele and Josephs (1990) as 'alcohol myopia'. This approach suggests that the impairment due to alcohol does not express itself uniformly on cognitive functioning, but results in a narrowing of attention which leaves the subject able to respond to the most salient cues, but greatly reduces the ability to deal with less salient or peripheral information. This pattern is especially significant when there is conflict between the two sources of information, and characteristic patterns of drunken behaviour may arise when the salient cues lead to, say, anger, while the expression of the anger is inhibited by less salient, but important, cues, such as an awareness of the likely consequences of the action. In the context of the Four-Choice task, the conflict is between going as fast as possible and avoiding errors. On this view, the inhibiting factor, the impending random stimulus, being less salient, would be expected to have less effect on performance when on alcohol than on placebo.

The intention in setting up the present version of the Four-Choice task was to provide an analogue of certain aspects of driving, in particular the fixed sequences representing routine, under-loaded periods, and the transition from fixed to random sequence representing the necessity to re-engage full attention after a period on 'automatic pilot'. If this analogy is valid, the combination of a tendency towards speeding up of responding rate, together with an impairment of information processing capacity is a particularly dangerous one. The sharp increase in error rates with ethanol supports this concern.

The pattern with temazepam, a tendency to slow down even when the task is under-loaded is quite distinct from that of ethanol, and would seem to be a less hazardous response to impairment. This may be reflected in the difficulty in demonstrating correlations between benzodiazepine use and traffic accidents. Impairments of information processing with normal therapeutic doses of benzodiazepines have been consistently shown to be at least as great as those with alcohol at around the UK legal limit for driving (80 mg/100 ml) (O'Hanlon *et al.*, 1986), a dose at which the increased accident risk with ethanol is readily demonstrated by a number of different methods (see e.g. Borkenstein *et al.*, 1964; Perrine, 1975; Robertson and Drummer, 1994). However, the relationship between benzodiazepines and accident risk remains controversial. Some studies have provided epidemiological evidence for such a link (e.g. Skegg *et al.*, 1979), while other studies have not (Benzodiazepine/Driving Collaborative Group, 1993). What seems clear is that any risk due to benzodiazepines is less than that associated with ethanol.

If a tendency to speed up under certain circumstances while impaired may be regarded as a form of drunken excess, it would be of great interest to compare benzodiazepines to ethanol on the types of measure of such excess discussed by Steele and Josephs (1990).

Memory

The effects of ethanol and temazepam are also quite distinct for the measure of long-term recall from the Buschke Selective Reminding Task, the impairment due to ethanol being about three times that for temazepam. This may seem surprising, in view of the number of studies suggesting specific effects of benzodiazepines on memory, but in fact few direct comparisons of benzodiazepines and other CNS depressants have been carried out. One study, that of Schuckit *et al.* (1991), claimed to show relatively greater effects of diazepam than ethanol on memory, as assessed by free recall of word lists. However, the effects of the ethanol dose in that study appears to have been less on all measures than the effects of the lower of the two diazepam doses used. This makes it very difficult to draw any conclusions about relative effects on different functions.

In a comparison of alprazolam and ethanol, Roache *et al.* (1993) achieved a much more satisfactory dose comparison. Their results do suggest a

greater effect of alprazolam than ethanol, particularly on a delayed recall of sequences of digits. The delay used was short, however, being 10 s, and there was no intervening activity, making direct comparisons with the measures used here difficult.

Several different aspects of memory are likely to be important in understanding drug-induced differences. The first is the comparison of acquisition and recall. The consensus here is that acquisition of new material is impaired by these drugs, but not retrieval. Indeed, in some circumstances, retrieval of material learned before drug administration can be enhanced. This phenomenon is known as retrograde facilitation, and generally attributed to the reduction of interference due to the drug (Summerfield and Steinberg, 1957; Ghoneim and Mewaldt, 1990; Tyson and Schirmuly, 1994).

A second distinction is that between short-term or primary memory and long-term or secondary memory. The terms long- and short-term tend to be misleading, since they imply that it is the interval between presentation of material and its recall that is most important. Baddeley (1986) has pointed out that long-term memory must be involved in performance on 'short-term' tasks, and that in the absence of interference, material can be retained for considerable intervals without being consolidated in the long-term store. Such a view was already implicit in the approach of earlier authors, including Buschke and Fuld (1974), who used resistance to disruption, not duration, as the key distinction between the two types of memory. Thus the selective reminding task may be particularly useful in this respect.

A third distinction is between episodic memory (memory for specific events) and semantic memory (knowledge of facts or of associations), the former being considered much more susceptible to changes in state than the latter (see e.g. Ghoneim and Mewaldt, 1990). There is a problem of interpretation here, however, because the semantic memories studied have generally been established ones. Since established memories are in general unaffected by benzodiazepines and ethanol, this finding may not be related to the episodic/semantic distinction. What is needed is studies on new semantic learning. There has been little drug-related work in this area.

The relationship of the Buschke test to the episodic/semantic distinction is not entirely clear. Word list recall is normally considered to tap episodic memory, but in tasks like the Buschke where a list is presented several times, the connection with a specific remembered event may not be close. Thus

word-learning tasks which require recall involving a specific presentation may also be useful.

Further studies involving both episodic memory and the learning of new semantic material would help to clarify these issues. These should involve direct dose-response comparisons between drugs of the type used here, and those by Roache *et al.* (1993), in order that any specific effects of different classes of drug on these types of memory can be firmly established.

ACKNOWLEDGEMENTS

This work was carried out in part-fulfilment of the requirements for BSc (Honours) degrees by Henry Faineteau, Arun Loganathan, Max Spiegelberg, and Zieda Taylor. Thanks are due to Dr Gordon Drummond, Department of Anaesthetics, for acting as Supervising Consultant.

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