Errors in performance testing: a comparison of ethanol and temazepam

B. Tiplady[1], J. Hiroz[2], L. Holmes[2] and G. Drummond[1]

Departments of [1]Anaesthesia Critical Care and Pain Medicine and [2]Neuroscience, University of Edinburgh, Edinburgh, UK.

Both ethanol and benzodiazepines impair psychomotor function. Previous work has suggested that ethanol may have a greater effect on errors while benzodiazepines may cause greater slowing, but this has not been tested in a direct comparison. We assessed the effects of ethanol, at blood concentrations of approximately 80–100 mg/100 ml, compared to two doses of temazepam (20 mg and 30 mg) on psychomotor speed and accuracy and on long-term memory. Sixteen healthy volunteers (eight male, aged 20–25 years) took part in a four-period, placebo-controlled cross-over study. Performance was evaluated using analysis of covariance (critical significance level, $p = 0.05$) comparing the areas under the response-time curves. Performance on a psychomotor maze showed an almost complete dissociation, with ethanol leading to a substantial and significant increase in errors with little effect on speed, while temazepam slowed performance with no significant change in accuracy. Other tasks showed a similar pattern, but the dissociation was less complete. Handwriting size was substantially increased by ethanol, but not by temazepam. Information processing capacity and long-term memory formation were reduced by a similar amount both for ethanol and 30 mg temazepam. The faster, more error-prone, behaviour on ethanol than with a similarly impairing dose of temazepam has clear implications for the relative potential of the two drugs to contribute to accidents. The results are also important in understanding the differential effects of drugs with different mechanisms of action on human performance.

Key words: ethanol, handwriting, memory, psychomotor errors, psychomotor speed, speed–accuracy trade-off, temazepam

Introduction

The effects of ethanol on cognitive and psychomotor function are well-known. Impairments to formation of new long-term memory, increased response times and an increase in errors or reduction in task accuracy are all seen at doses well within the range of social drinking (Wallgren and Barry, 1970; Hindmarch *et al*., 1991; Cameron *et al*., 2001). These effects are similar in many respects to those found with other central nervous system (CNS) depressants; for example, benzodiazepines and anaesthetics (Block *et al*., 1988; Curran and Birch, 1991; Kunsman *et al*., 1992).

These drugs do not necessarily share the same mechanisms. For example, the benzodiazepines act primarily by enhancing inhibitory transmission at the $GABA_A$ receptor, while ethanol and nitrous oxide affect other receptors, in particular inhibiting excitatory amino acid transmission at the *N*-methyl-D-aspartate (NMDA) receptor (Mihic *et al*., 1997; Wang *et al*., 1999). Other drugs with different mechanisms such as inhibitors of cholinergic and noradrenergic transmission are also CNS depressants (Broks *et al*., 1988). These different types of drugs often have distinct subjective effects in humans, and also show discriminative stimulus properties in animal experiments (Engel *et al*., 2001; Hodge *et al*., 2001).

It might therefore be expected that the objective performance effects would also show distinct profiles. However, in spite of the volume of work on performance effects of CNS depressant drugs, relatively few studies have directly compared the effects of ethanol on different aspects of performance with other classes of drug. There is a considerable literature on the interactions of drugs of various kinds with ethanol (Linnoila *et al*., 1979; Allen *et al*., 1988; Kerr and Hindmarch, 1998). However, these studies have generally been concerned with the magnitude of impairment, not with profiles of drug action, and neither the selection of tests used nor the presentation of results makes it easy to make comparisons between ethanol and the other drugs investigated.

Several studies have compared the effects of ethanol directly to those of other classes of drugs, with most concentrating on memory. Roache *et al*. (1993a) investigated various doses of triazolam (maximum 8 µg/kg) and ethanol (maximum 1 g/kg). The effect of the two drugs on psychomotor performance was similar, but ethanol had less effect on memory as measured by digit-span test and picture recognition. In another comparison of triazolam with ethanol (Roache *et al*., 1993b), both drugs impaired performance on a matching to sample task using checkerboard-like patterns, and both speed and accuracy components of the task were affected. Triazolam appeared to slow response times more than ethanol, while ethanol had more effect on accuracy, but this possibility was not formally tested.

Similar effects on task accuracy have been seen in comparisons of ethanol with temazepam. Tiplady *et al.* (1998) compared ethanol (maximum 0.88 g/kg) and temazepam (maximum 20 mg) in a dose–response study. The two drugs increased response times on a four-choice reaction task to a similar degree, while error rates increased only after ethanol. A similar trend was seen for a symbol-digit matching task, although in this case the error scores did not show significant differences (Tiplady *et al.*, 1999).

A difficulty with using error scores in psychomotor tasks is that error rates are generally low, and some subjects may make no errors at all. Thus, when overall degree of impairment is the main issue, error rates are often ignored. Nevertheless, when profiles of drug action are of interest, all aspects of performance should be considered. Different types of test could allow a more reliable assessment of errors. For example, overloaded tests, such as rapid visual information processing (Wesnes and Warburton, 1983), or tests involving distractors (Eriksen and Eriksen, 1974) may provide greater and more consistent error rates which are easier to treat statistically.

One type of task that we have investigated recently is the psychomotor maze. This type of task is traditionally carried out using paper (Gibson, 1978), but the introduction of pen computers has allowed easy automation of these tasks. Strictly speaking these are not mazes as there is a single track marked on the test sheet which the volunteer follows with the pen as quickly as possible without touching the sides. Studies comparing paper and electronic versions of these tasks showed that ethanol produced large increases in error scores, with comparatively little slowing (Cameron *et al.*, 2001). No direct comparison of the effects of ethanol with other classes of drug has yet been made for this type of task.

We have compared the effects of ethanol and temazepam on a range of attention and psychomotor tasks, including mazes, handwriting, digit-symbol matching and tasks with distractors. In view of the interest in benzodiazepines and memory, we also assessed working memory and long-term memory formation.

Methods

Design
We used a randomized, double-blind, four-period design. Volunteers took part in four sessions, at least 2 days apart, in which they received by mouth either (i) placebo; (ii) temazepam 20 mg; (iii) temazepam 30 mg; or (iv) ethanol, calculated to produce peak blood alcohol concentrations in the range 80–100 mg/100 ml, as single doses. The order of administration was assigned using Williams squares to give a variance-balanced design (Williams, 1949). Performance testing and subjective ratings were carried out before treatment and at intervals over the next 3 h.

Subjects
Volunteers gave their written informed consent to take part in the study, which was approved by the ethics committee of the Lothian Health Board. Sixteen volunteers (eight male, eight female) aged 20–25 years (mean 22) and weighing 50–83 kg (mean 68.3) were recruited. All were healthy as assessed at initial screening, were light to moderate social drinkers (reported alcohol consumption 5–30 units/week; mean 16.6), had negative pregnancy tests if female, and were not taking any medication that might have interfered with CNS function or drug absorption or elimination.

Assessments
The test battery lasted approximately 30 min, and consisted of the tests outlined below.

Number Pairs (Attention)
In each trial, a set of five digits appeared in a row on the computer screen. The task was to determine if the second and fourth digits were the same, and tap a 'Yes' button if so, a 'No' button otherwise, ignoring the other three distractor digits. One hundred and sixty trials were presented, and the reaction times for correct responses and the number of errors were recorded.

Spiral Maze (Psychomotor: Gibson, 1978)
This maze consisted of a white path bounded by a black spiral, with circular obstacles. The pencil was placed at the centre of the spiral and the path traced around the spiral as rapidly as possible while avoiding the black sides and the obstacles. Time taken was recorded with a stopwatch. The error score was calculated as described by Gibson (1978), scoring minor errors (line touching the side or obstacle) as 1 point, and major errors (line penetrating the side or obstacle) as 2 points.

Rectangular Maze (Psychomotor: Cameron et al., 2001)
A light path appeared on the pen computer screen against a dark background. The volunteer started with the pen at the top left corner of the screen. When a bell sounded, the volunteer traced the path to the bottom left corner as quickly as possible, while trying to stay within the light track. The time taken and the number of errors (occasions when the pen left the track) were recorded.

Handwriting (Psychomotor: Legge et al., 1964)
Volunteers wrote four specified words one at a time on the computer screen. The length and height of each written word was taken.

Digit-Symbol Substitution (Psychomotor/Cognitive: Wechsler, 1958; Cameron et al., 2001)
In this pencil-and-paper task, there was a key which matched nine symbols to the digits 1–9. Below this, there was a series of random digits with a box beneath each digit in which the subject wrote the corresponding symbol as quickly as possible. The number of symbols correctly substituted in 90 s and the number of errors were recorded.

Digit-Symbol Matching (Psychomotor/Cognitive: Mattila and Mattila-Evenden, 1997; Cameron et al., 2001)
In this computerized version of the Digit-Symbol Substitution Test, there was a key which matched nine symbols to the digits 1–9. Below this, there were two boxes in which were presented a digit-symbol pair. If the pair corresponded to a match in the key table, the subject tapped a 'Yes' button, if not, a 'No' button, as quickly as possible. Fifty trials were presented, and the reaction times for correct responses and the number of errors were recorded

Selective Reminding (New Memory Formation)
The experimenter read a list of 15 words to the volunteer, who then

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

Memory Scanning *(Working Memory Access: Sternberg, 1975)*

A set of three digits appeared on the computer screen, which the volunteer memorized. Following this, a series of digits appeared one at a time, and the volunteer tapped a 'Yes' button if the digit was in the memorized set, a 'No' otherwise. The procedure was repeated with sets of four and five digits. Response times and numbers of errors were recorded.

Visual Analogue Sales (VAS: Mood)

Each scale consisted of a 10-cm line displayed on the computer screen, the ends of which were marked with antonyms (e.g. Alert–Drowsy). Subjects made a mark on the line to indicate how they felt at that moment. The 16 scales described by Bond and Lader (1974) were used, together with Sober–Drunk.

Equipment

All tests were carried out on the Apple MessagePad MP2000 (Apple Computer, Inc., Cupertino, CA, USA) except for the Spiral Maze and Digit-Symbol Substitution, which were pencil and paper, and Selective Reminding, which was administered verbally. Digit-Symbol Substitution, Selective Reminding and the Rectangular Maze were available in multiple versions. The single published version of the Spiral Maze was used (Gibson, 1978). Other test materials were generated randomly for each time point. Blood alcohol concentrations were estimated using a breathalyser (Lion Alcolmeter, Lion Laboratories, Barry, UK).

Procedures

Each volunteer first took part in a familiarization session in which the test procedures were demonstrated and all tests were carried out at least three times.

Volunteers then took part in four afternoon sessions. 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 24 h after dosing. 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 dosing (baseline). Volunteers then received a capsule containing 20 or 30 mg of temazepam, or placebo (lactose), and a drink containing vodka or water mixed with an equal volume of orange juice. Ethanol doses were 0.8 g/kg, up to a maximum of 66 g, for males, and 0.7 g/kg, up to a maximum of 55 g for females. The difference in dose for males and females was designed to obtain approximately equal target blood ethanol concentrations (Mumenthaler *et al*., 1999). The taste of the drink was masked by giving a Tyrozet® lozenge to suck for 1 min , and by spraying the drink with a peppermint breath freshener. The drink was consumed within 10 min. The test battery was then administered at 45, 90 and 165 min post-drug, these times representing the mid-points of the testing periods. Selective Reminding was carried out only at the 45-min time-point. Selective Reminding was carried out only once during each test session to avoid the possibility of interference occurring between different lists of words.

Breathalyser readings were taken before the drink and at the beginning and end of the each administration of the test battery.

Statistical analysis

For the Digit-Symbol Yes-No task and the Number Pair task, mean response times and error scores were analysed, as well as the information transfer rate. The information per response, I, was computed using the formula:

$$I = 2 - [(1 - E)\log(1/[0.5(1 - E)]) + E\log(1/0.5E)]$$

where E is the proportion of errors (0–1) and logarithms are to base 2 (Welford, 1980). The information transfer rate (ITR) was then given by I/RT, where RT is the mean response time in seconds. The ITR allows an assessment of the overall performance (ability) on a task that takes both speed and errors into account. Thus, a single measure of impairment due to a treatment can be used when both speed and accuracy of performance are affected.

Visual analogue scales were grouped into two factors closely similar to those described by Herbert *et al*. (1976). (i) Functional Integrity: drowsy, feeble, muzzy, clumsy, lethargic, mentally slow, dreamy, incompetent, bored; (ii) Mood: excited, discontented, troubled, tense, sad, antagonistic, unsociable (Cameron *et al*., 2001). In addition the Alert–Drowsy, Incompetent–Proficient and Sober–Drunk scales were analysed individually.

Data were first analysed to check for carryover effects using Analysis of Variance on the baseline (pre-dose) assessment. In the absence of significant effects of previous treatment, the main analysis for all test measures except Selective Reminding used area under the response–time curve, from 0 to 165 min post-dose, calculated using the trapezoid rule. Values were then normalized so that the resulting units corresponded to the units of the original measurements. The area under the curve was used to provide a summary measure of overall drug effect which would allow comparison between drugs that might have somewhat different pharmacokinetic profiles. For the Selective Reminding test, the single post-dose assessment was used.

Analysis of covariance (PROC GLM in SAS statistical software package; SAS Institute, Cary, NC, USA) with pre-dose score as a covariate was used to determine whether an overall treatment effect was present. Pairwise comparisons were made using the Tukey–Kramer correction for multiplicity. For Selective Reminding, no pre-dose assessment was made, and a simple analysis of variance was therefore used. $p < 0.05$ was considered statistically significant.

Results

Mean blood alcohol concentrations estimated from the breath measurements in the ethanol condition were 94.2 mg/100 ml (SD 26.3) for the 45-min assessment, 95.8 mg/100 ml (SD 20.6) at 90 min, and 56.9 mg/100 ml at 165 min.

Data from the performance tests and visual analogue scales are shown in Table 1. All objective test measures showed significant

Table 1 Data from objective measures and visual analogue scales

	Area under the response/time curve (AUC)					
	Placebo	Temazepam (20 mg)	Temazepam (30 mg)	Ethanol	*F*-value	SE of difference[a]
Digit Symbol Substitution (Paper)						
Total n correct	79.3	71.3	68.8	69.1	23.84	1.45
p versus Placebo		0.0001	0.0001	0.0001		
p versus Temazepam (20 mg)			0.3299	0.409		
p versus Temazepam (30 mg)				0.9977		
n **Incorrect**	0.33	0.75	0.55	1.59	6.41	0.318
p versus Placebo		0.5559	0.8843	0.0011		
p versus Temazepam (20 mg)			0.9237	0.0511		
p versus Temazepam (30 mg)				0.0087		
Digit Symbol Matching						
RT Correct (s)	1.35	1.42	1.53	1.37	4.69	0.052
p versus Placebo		0.4853	0.0084	0.9845		
p versus Temazepam (20 mg)			0.1911	0.7016		
p versus Temazepam (30 mg)				0.0167		
n **Incorrect**	2.22	2.13	2.51	3.66	3.84	0.59
p versus Placebo		0.998	0.9415	0.0336		
p versus Temazepam (20 mg)			0.8774	0.0252		
p versus Temazepam (30 mg)				0.1232		
Information Transfer (bit/s)	0.596	0.562	0.503	0.495	6.36	0.027
p versus Placebo		0.6103	0.0083	0.0031		
p versus Temazepam (20 mg)			0.1463	0.0817		
p versus Temazepam (30 mg)				0.9904		
Gibson Spiral Maze (Paper)						
Total Time (s)	21.9	25.4	27.5	22.3	16.36	0.93
p versus Placebo		0.0012	0.0001	0.9504		
p versus Temazepam (20 mg)			0.1041	0.0063		
p versus Temazepam (30 mg)				0.0001		
Error Score	18.3	18.2	16.9	26.8	8.69	2.21
p versus Placebo		0.9999	0.9229	0.0023		
p versus Temazepam (20 mg)			0.9411	0.0015		
p versus Temazepam (30 mg)				0.0003		
Rectangular Maze						
Total Time (s)	18.5	19.7	21.9	17.7	3.59	1.37
p versus Placebo		0.8146	0.0777	0.9177		
p versus Temazepam (20 mg)			0.3779	0.4439		
p versus Temazepam (30 mg)				0.0169		
n **Errors**	4.83	6.14	6.06	8.22	4.09	1.00
p versus Placebo		0.553	0.6127	0.0069		
p versus Temazepam (20 mg)			0.9998	0.1741		
p versus Temazepam (30 mg)				0.1526		
Number Pairs						
RT Correct (s)	0.772	0.821	0.859	0.808	12.6	0.0147
p versus Placebo		0.0079	0.0001	0.0736		
p versus Temazepam (20 mg)			0.0591	0.7995		
p versus Temazepam (30 mg)				0.0057		
n **Incorrect**	1.56	1.56	2.03	3.21	6.15	0.451
p versus Placebo		1	0.7074	0.0028		
p versus Temazepam (20 mg)			0.7052	0.0033		
p versus Temazepam (30 mg)				0.0578		
Information Transfer (bit/s)	1.21	1.15	1.08	1.10	19.5	0.020
p versus Placebo		0.0055	0.0001	0.0001		
p versus Temazepam (20 mg)			0.0128	0.0677		
p versus Temazepam (30 mg)				0.8733		
Memory Scanning						
RT Correct (s)	0.711	0.783	0.837	0.762	9.51	0.0249
p versus Placebo		0.0235	0.0001	0.1877		
p versus Temazepam (20 mg)			0.1205	0.8454		
p versus Temazepam (30 mg)				0.0191		
n **Incorrect**	5.29	6.46	9.38	9.68	4.25	1.584
p versus Placebo		0.8583	0.0396	0.0293		
p versus Temazepam (20 mg)			0.2071	0.192		
p versus Temazepam (30 mg)				0.9975		
Writing						
Word Length (mm)	58.4	58.0	57.2	64.1	3.58	2.42
p versus Placebo		0.9983	0.9538	0.1018		
p versus Temazepam (20 mg)			0.9851	0.0593		
p versus Temazepam (30 mg)				0.0304		

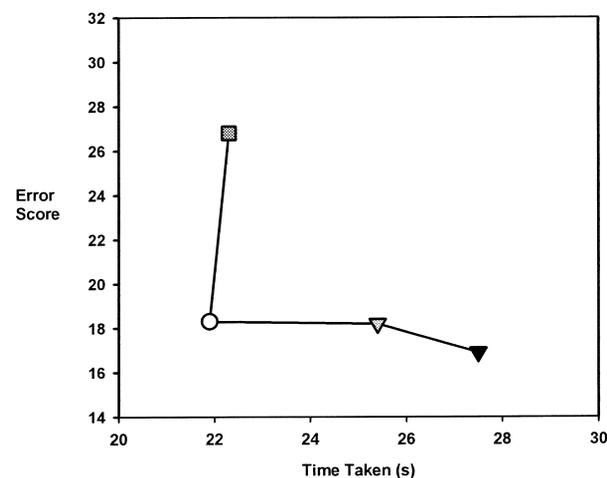|	Placebo	Temazepam (20 mg)	Temazepam (30 mg)	Ethanol	F-value	SE of difference[a]
Area under the response/time curve (AUC)						
Word Height (mm)	25.0	25.0	25.3	27.7	4.04	0.947
p versus Placebo		1	0.9892	0.0323		
p versus Temazepam (20 mg)			0.986	0.0189		
p versus Temazepam (30 mg)				0.0545		
Selective Reminding						
Short-term Memory	27.7	31.3	25.9	27.4	0.32	5.73
p versus Placebo		0.9248	0.9883	0.9999		
p versus Temazepam (20 mg)			0.7822	0.9037		
p versus Temazepam (30 mg)				0.9936		
Long-term Memory (/90)	67.6	57.3	49.9	52.5	6.16	4.45
p versus Placebo		0.1103	0.0015	0.0078		
p versus Temazepam (20 mg)			0.3587	0.7027		
p versus Temazepam (30 mg)				0.9388		
Long-term Forgetting	2.56	3.62	4.81	4.25	2.25	0.909
p versus Placebo		0.6498	0.0789	0.2625		
p versus Temazepam (20 mg)			0.5645	0.9014		
p versus Temazepam (30 mg)				0.9256		
Visual Analogue Scales						
Factor I: Functional Integrity	33.6	46.9	52.5	43.6	14.9	3.01
p versus Placebo		0.0002	0.0001	0.0061		
p versus Temazepam (20 mg)			0.2701	0.667		
p versus Temazepam (30 mg)				0.0184		
Factor II: Mood	29.6	27.1	29.1	27.3	1.06	1.87
p versus *P*lacebo		0.4911	0.9918	0.5688		
p versus Temazepam (20 mg)			0.6802	0.9998		
p versus Temazepam (30 mg)				0.7244		
Alert–Drowsy	30.1	48.2	54.9	43.7	15.2	3.89
p versus Placebo		0.0001	0.0001	0.0043		
p versus Temazepam (20 mg)			0.3276	0.6346		
p versus Temazepam (30 mg)				0.0249		
Incompetent–Proficient	67.7	55.8	52.8	57.5	31.4	3.68
p versus Placebo		0.0072	0.0013	0.0323		
p versus Temazepam 20 mg)			0.8342	0.9594		
p versus Temazepam (30 mg)				0.5247		
Sober–Drunk	12.4	22.3	24.4	51.9	3.14	4.27
p versus Placebo		0.1074	0.0356	0.0001		
p versus Temazepam (20 mg)			0.9609	0.0001		
p versus Temazepam (30 mg)				0.0001		

AUC figures are mean values of the normalized areas under the response-time curve, calculated using the formula
AUC = $(45V_b + 90V_1 + 120V_2 + 75V_3)/330$ where V_b is value at baseline, V_1 is value at time-point 1, etc. [a]SE of the differences between treatment means for the pairwise comparisons. *p*-values were adjusted for multiplicity using the Tukey–Kramer method.

overall effects of treatment except short-term recall and forgetting from long-term memory in the Selective Reminding task. Information transfer rates for Digit-Symbol Matching and Number Pairs indicated that the overall degree of impairment for ethanol and the large dose of temazepam was similar, with less impairment (significant for number pairs) being found at the smaller dose of temazepam.

The large dose of temazepam slowed responses in all speeded measures, except the rectangular maze, while the smaller dose significantly slowed responses for the Spiral Maze, Number Pairs, Memory Scanning and Digit-Symbol Substitution.

The only error measure to be affected by temazepam was Memory Scanning, at the larger dose. Ethanol led to significantly slower performance only in Digit-Symbol Substitution, but significantly increased all error measures. Errors were significantly higher for ethanol than for the large dose of temazepam in the error measures from Digit Symbol Substitution and Spiral Maze. The effects of the two drugs on speed and errors in the Spiral Maze are shown in Figure 1, for Number Pairs in Figure 2, and for Memory Scanning in Figure 3.
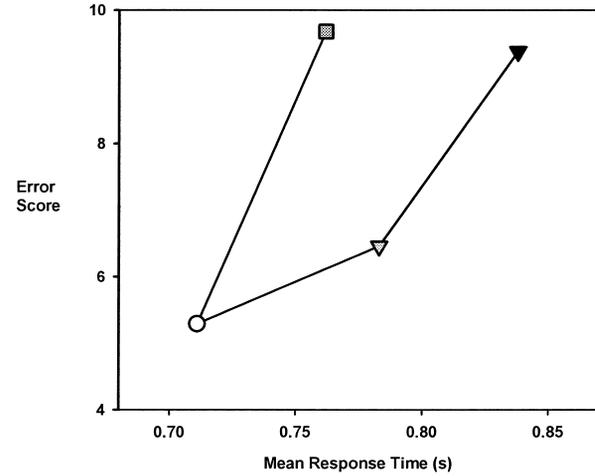
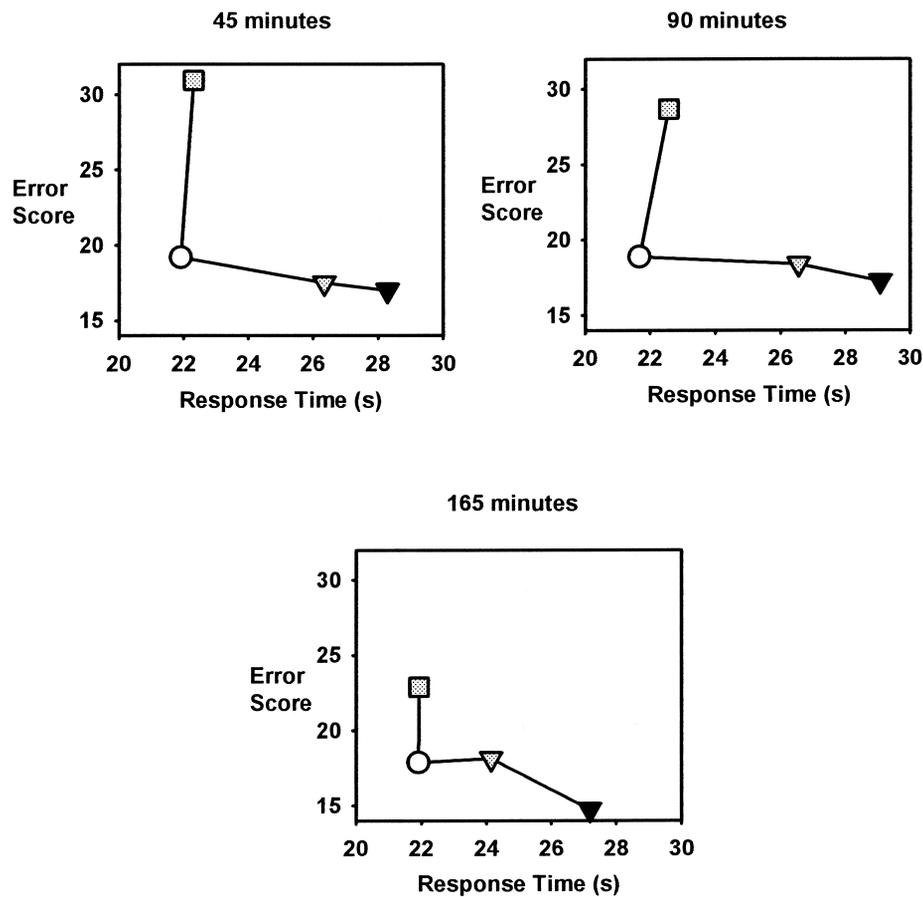The time-course of the effects on the Spiral Maze is shown in

Figure 1 Speed–Accuracy plot for the Gibson Spiral Maze. Open circle: placebo; light grey triangle: temazepam 20 mg; black triangle: temazepam 30 mg; grey square: ethanol. Values for time taken and error score are the areas under the response-time curve (to 165 min) normalized to correspond to the original scoring.
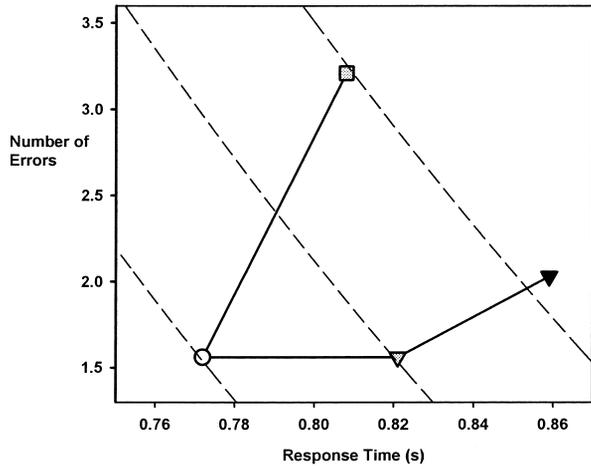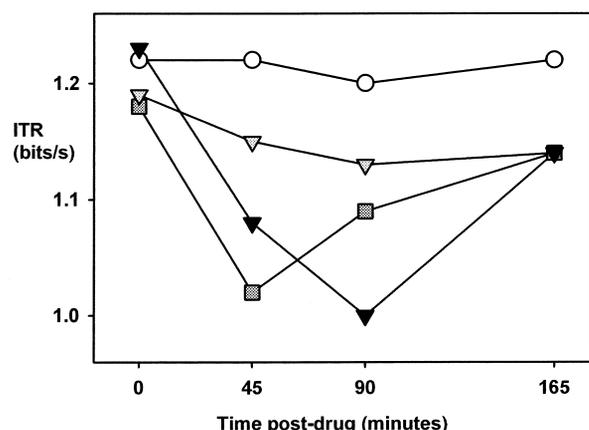
Figure 2 Speed–Accuracy plot for the Number Pairs Task. Open circle: placebo; light grey triangle: temazepam 20 mg; black triangle: temazepam 30 mg; grey square: ethanol. Values for time taken and error score are the areas under the response-time curve (to 165 min) normalized to correspond to the original scoring. Dashed lines indicate iso-information contours for different information transfer rates.

Figure 3 Speed–Accuracy plot for the Memory Scanning Task. Open circle: placebo; light grey triangle: temazepam 20 mg; dark grey triangle: temazepam 30 mg; grey square: ethanol. Values for time taken and error score are the areas under the response-time curve (to 165 min) normalized to correspond to the original scoring.

Figure 4 Speed–Accuracy plots for the Gibson Spiral Maze at the individual assessment time-points. Open circle: placebo; light grey triangle: temazepam 20 mg; black triangle: temazepam 30 mg; grey square: ethanol

factor was not significantly affected by either drug.

Figure 5 Time course of the effects on Information Transfer Rate (ITR) for the Number Pairs task. Open circles: placebo; light grey triangles: temazepam 20 mg; black triangles: temazepam 30 mg; grey squares: ethanol

Figure 4. The pattern of results is consistent over all three time-points, with ethanol affecting errors, and temazepam affecting speed. The time-course of the effects on Information Transfer Rate in the Number Pairs task is shown in Figure 5. The peak effects of ethanol are found at the 45-min assessment, those of temazepam at 90 min. Both drugs were past their peak effects at 165 min post-dose.

Both drugs decreased long-term recall on the Selective Reminding task. Ethanol, but not temazepam, substantially increased both the length and height of handwritten words.

The visual analogue scales showed that both drugs showed impairments to the ratings of functional integrity, decreased ratings of proficiency, and increased ratings of drunkenness and drowsiness. Ethanol had a significantly greater effect on drunkenness than temazepam, while the reverse was found for drowsiness (Figure 6). Results for the Functional Integrity factor were similar to those for the Alert–Drowsy scale, while the Mood
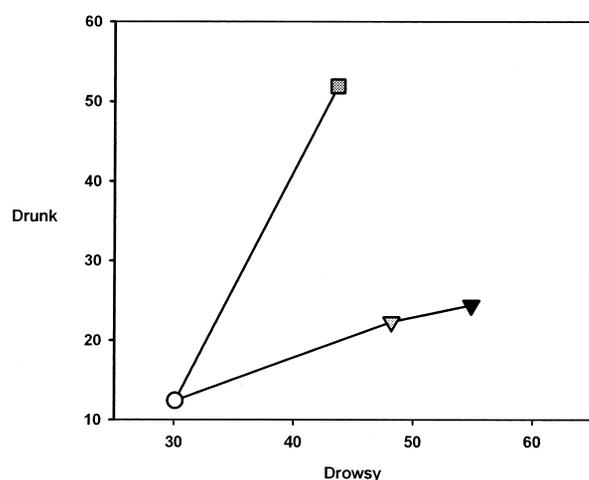
Figure 6 Plot of scores on the Alert–Drowsy Visual Analogue Scale against scores on Sober–Drunk. Open circle: placebo; light grey triangle: temazepam 20 mg; dark grey triangle: temazepam 30 mg; grey square: ethanol. Values are the areas under the response-time curve (to 165 min) normalized to correspond to the original scoring.

Discussion

These results show a clear double dissociation between the effects of ethanol and temazepam, both on objective and subjective measures of drug effect. Ethanol consistently led to a higher rate of errors in psychomotor tasks, and to greater reported drunkenness than temazepam, while slowing of responses and subjective drowsiness were more marked with temazepam.

This type of dissociation can be illustrated effectively using a graph in which the number of errors made in each drug condition is plotted against the corresponding mean response time (Figures 1–4). Such plots have most often been used for presenting speed–accuracy trade-off curves (Schouten and Becker, 1967; Tiplady *et al*., 2001), but are also particularly helpful in comparing the speed-accuracy profiles of different drugs in dose–response studies. Dissociation on such graphs is shown by a divergence between the lines from placebo for the two drugs. Similar graphs may be used to illustrate the differential subjective effects of the two drugs (e.g. by plotting reported drunkenness against drowsiness for the various drug conditions) (Figure 6).

The difference between the effects of ethanol and temazepam can be seen most clearly with the Spiral Maze task (Figures 1 and 4). In this case, the divergence is almost complete, the two lines being at approximately 90° to each other. The divergence for Number Pairs is less complete, but still very clear (Figure 2), indicating that the trend for ethanol to cause a relatively greater increase in errors than temazepam is not limited to maze tasks.

Figure 2 also illustrates the relationship between the speed–accuracy divergence and the speed–accuracy trade-off (SATO). Within limits, speed and accuracy can be traded off against each ether, with fast performance being associated with high error rates, and slow performance with lower errors. The particular trade-off adopted depends, among other things, on the personality of the person performing the task, instructions given as to the importance of speed and accuracy, feedback, or explicitly giving rewards or penalties for fast or accurate performance The dashed lines in the graph in Figure 2 represent iso-information contours, connecting points with the same value of information transfer rate. Each contour thus represents an approximate SATO curve for a particular level of ability. The points for ethanol and the large dose of temazepam have similar values of ITR (Table 1) and lie close to the same SATO curve. Thus, at a doses causing a comparable degree of impairment, ethanol leads to faster, more error-prone behaviour than temazepam.

The data from the Spiral Maze task at the individual assessment points (Figure 4) shows a similar pattern at all the time points. Thus the dissociation between speed and accuracy is stable, and not significantly affected by differences between ascending and descending phases of the response curve.

The doses of temazepam used here were chosen to be within the range of clinical use (initial recommended daily dose 10–30 mg) while being well-tolerated by volunteers (Begg *et al*., 2001). The dose of ethanol is close to the maximum that is well-tolerated by volunteers (Fagan, 1991). Given the differences in the two drugs and the way they are used, it is necessary to consider whether the doses compared were appropriate, and whether, for example, the differences observed might be a function of dose rather than of

differences in pharmacology. This seems very unlikely for three reasons. First, the overall impairment to information transfer rate produced by ethanol and the larger dose of temazepam are closely comparable (Table 1). Second, lower doses of both drugs than those used here have been used in previous studies, and shown to cause less impairment but with similar qualitative patterns of change (Tiplady *et al*., 1999, 2001). Thus, the pattern of differences in speed error profile appears to hold true over a range of doses. Third, the differences shown here represent a double dissociation between the effects on speed and errors, a finding which is extremely difficult to account for in terms of dose. Thus, it is unlikely that the differences found here can be explained by an inappropriate dose comparison.

In contrast to the psychomotor measures, the Memory Scanning task showed much less difference between the two drugs in the pattern of effects (Fig. 3). Significant slowing and an increase in errors were seen for both ethanol and temazepam, and the number of errors for the larger dose temazepam was similar to that for ethanol. This may reflect a difference in the nature of the tasks. While, in the Digit-Symbol and Number Pair tasks, it is always possible for the volunteer to respond correctly if enough time is taken, taking longer to respond may not help in the Memory Scanning task if the volunteer has forgotten if the digit is in the set or not. There is auditory feedback (a 'beep') to errors in this task, giving the volunteer a reminder, but this only occurs once the error has been made. Thus, ethanol and the large dose of temazepam appear to cause a similar degree of disruption to working memory function as assessed by the Memory Scanning task.

Selective Reminding also showed very similar results for ethanol and the large dose of temazepam, with the two drugs causing similar impairment to long-term memory formation, a non-significant trend to increased forgetting from long-term memory, and no change in short-term memory.

Taken together, these results indicate that, at doses leading to very similar impairment to memory and to the overall rate of information processing, temazepam and ethanol differ greatly in their effect on psychomotor performance, with ethanol leading to faster, more error-prone behaviour than temazepam. This finding is of considerable practical and theoretical significance.

The practical issues relate particularly to accidents. There is now clear evidence from prescription data that benzodiazepines are associated with an increased risk of crashes (Barbone *et al*., 1998), an effect found principally with anxiolytics such as diazepam rather than hypnotic drugs such as temazepam. The former drugs have longer half-lives, and are likely to be taken during the day rather than just at night. Thus, the difference between the two classes of benzodiazepine is likely to reflect differences in plasma concentration at the time of driving rather than in their mode of action. The risks associated with ethanol and driving have of course been established for many years (Borkenstein *et al*., 1964; Robertson and Drummer, 1994).

Speed is clearly a factor in accidents (Elander *et al*., 1993), and the question arises as to whether the differential effects of drugs on speed of performance and errors in laboratory tests might be relevant to real driving behaviour. In most studies of the effects of drugs on driving, volunteers are instructed to maintain a particular speed. However, real driving is to a large degree self-paced, and the speed chosen depends among other things on the driver's perception of risk, and judgements concerning road and traffic conditions (for a review, see Ranney, 1994). Where speed has been investigated as a dependent variable, no change in driving speed has been observed with ethanol (West *et al*., 1993), nor has any effect on speed perception been seen (Kearney and Guppy, 1988). However, no comparative studies have been reported in this area, and comparisons of speed and errors in real driving under the influence of different drugs would be of great interest.

The theoretical interest is in the opportunity this difference offers for studying the mechanisms of drug action on the central nervous system. A clear divergence, such as that found here between ethanol and temazepam, may relate to the differences between the drugs in their actions on receptors in the CNS. Investigating the speed-accuracy profiles of drugs with selective actions on different neurotransmitters will provide useful information. One action of ethanol not shared with benzodiazepines is inhibition of NMDA receptor function, and this could warrant further investigation. Studies on selective NMDA antagonists such as ketamine have showed impairment to psycho-motor performance and memory (Harborne *et al*., 1996; Hetem et., 2000), but no studies have looked specifically at errors in psycho-motor tasks, and this would be of great value. The subjective effects of ketamine do not appear to be identical to those of ethanol, but may resemble ethanol to some degree (Bowdle *et al*., 1998; Krystal *et al*., 1998). It would be interesting to know if the subjective effects of such agents include feelings of being drunk.

The action of ethanol on handwriting size also has theoretical interest. Nitrous oxide also affects this measure, increasing the size of written words (Legge *et al*., 1963), while temazepam has virtually no effect. Nitrous oxide resembles ethanol in its actions on both $GABA_A$ and NMDA receptors. Investigating the effects of selective NMDA antagonists on handwriting would therefore also be of value. The implementation of the handwriting assessment used here was an extremely simple one, designed to assess whether the effects observed by Legge *et al*. (1963) could be repeated with ethanol. Future work should evaluate other aspects of handwriting (e.g. writing speed and the relationship between velocity and curvature of the strokes, and the effects of spatial working memory on writing speed). The effects of both ethanol and selective NMDA inhibitors on such parameters will be of interest.

The clear differences shown here between the effects of ethanol and temazepam on psychomotor performance will help to place the study of the mechanism and consequences of the distinctive effects of ethanol on a much firmer basis.

Acknowledgement

Address for correspondence

Brian Tiplady
AstraZeneca UK Clinical Research Group
10 Logie Mill
Logie Green Road
Edinburgh EH7 4HG
UK
Email: brian.tiplady@astrazeneca.com

References

Allen D, Lader M, Curran H V (1988) A comparative study of the interactions of alcohol with amitriptyline, fluoxetine and placebo in normal subjects. Neuropsychopharmacol Biol Psychiatry *12*: 63–80

Barbone F, McMahon A D, Davey P G, Morris A D, Reid I C, McDevitt D G, MacDonald T M (1998) Association of road-traffic accidents with benzodiazepine use. Lancet *352*: 1331–1336

Begg A, Drummond G, Tiplady B (2001) Effects of temazepam on memory and psychomotor performance: a dose–response study. Hum Psychopharmacol *16*: 475–480

Block R I, Ghoneim M M, Hinrichs J V, Kumar V (1988) Effects of a subanaesthetic concentration of nitrous oxide on memory and subjective experience: influence of assessment procedures and types of stimuli. Hum Psychopharmacol *3*: 257

Bond A, Lader M (1974) The use of analogue scales in rating subjective feelings. Br J Med Psychol *47*: 211–218

Borkenstein R F, Crowther R F, Shumate R P, Ziel W B, Zylman R (1964) Role of the drinking driver in traffic accidents. University of Indianna, Bloomington

Bowdle T A, Radant A D, Cowley D S, Kharasch E D, Strassman R J, Roy-Byrne P P (1998) Psychedelic effects of ketamine in healthy volunteers: relationship to steady-state plasma concentrations. Anesthesiology *88*: 82–88

Broks P, Preston G C, Traub M, Poppleton P, Ward C, Stahl S M (1988) Modelling dementia: effects of scopolamine on memory and attention. Neuropsychologia *26*: 685–700

Buschke H, Fuld P A (1974) Evaluating storage, retention and retrieval in disordered memory and learning. Neurology *24*: 1019–1025

Cameron E, Sinclair W, Tiplady B (2001) Validity and sensitivity of a pen computer battery of performance tests. J Psychopharmacol *15*: 105–110

Curran H V, Birch B (1991) Benzodiazepines, memory and mood; a review. Psychopharmacology *105*: 1

Elander J, West R, French D (1993) Behaviour correlates of individual differences in road traffic crash risk – an examination of methods and findings. Psychol Bull *113*: 279–294

Engel S R, Purdy R H, Grant K A (2001) Characterization of discriminative stimulus effect of the neuroactive steroid pregnanolone. J Pharmacol Exp Therap *297*: 489–495

Eriksen B A, Eriksen C W (1974) Effects of noise letters upon identification of target in a non-search task. Perception and Psychophysics *16*: 143–149

Fagan D (1991) Pharamcokinetics and pharmacodynamics of centrally acting depressants in man. PhD, University of Edinburgh

Gibson HB (1978) Manual to the Gibson spiral maze, 2 edn. Hodder and Stoughton Educational, Sevenoaks

Harborne G C, Watson F L, Healy D T, Groves L (1996) The effects of sub-anaesthetic doses of ketamine on memory, cognitive performance and subjective experience in healthy volunteers. J Psychopharmacol *10*: 134–140

Herbert M, Johns M W, Dore C (1976) Factor analysis of analogue scales measuring subjective feelings before and after sleep. Br J Med Psychol *49*: 373–379

Hetem L A B, Danion J M, Diemunsch P, Brandt C (2000) Effect of a subanesthetic dose of ketamine on memory and conscious awareness in human volunteers. Psychopharmacology *152*: 283–288

Hindmarch I, Kerr J S, Sherwood N (1991) The effects of alcohol and other drugs on psychomotor performance and cognitive function. Alcohol Alcoholism *26*: 71–79

Hodge C W, Cox A A, Bratt A M, Camariini R, Iller K, Kelley S P, Mehmert K K (2001) The discriminative stimulus properties of self-administered ethanol are mediated by GABA(A) and NMDA receptors in rats. Psychopharmacology (Berlin) *154*: 13–22

Kearney S A, Guppy A (1988) The effects of alcohol on speed perception in a closed course driving situation. J Studies Alcohol *49*: 340

Kerr J S, Hindmarch I (1998) The effects of alcohol alone or in combination with other drugs on information processing, task performance and subjective responses. Hum Psychopharmacol *13*: 1–9

Krystal J H, Petrakis I L, Webb E, Cooney N L, Karper L P, Namanworth S, Stetson P, Trevisan L A, Charney D S (1998) Dose-related ethanol-like effects of the NMDA antagonist, ketamine, in recently detoxified alcoholics. Arch Gen Psychiatry *55*: 354–360

Kunsman G W, Manno J E, Manno B R, Kunsman C M, Przekop M, A. (1992) The use of microcomputer-based psychomotor tests for the evaluation of benzodiazepine effects on human performance: a review with emphasis on temazepam. Br J Clin Pharmacol *34*: 289–301

Legge D, Steinberg H, Summerfield A (1964) Simple measures of handwriting as indices of drug effects. Percept Motor Skills *18*: 549–558

Linnoila M, Mattila M J, Kitchell B S (1979) Drug interactions with alcohol. Drugs *18*: 299

Mattila M J, Mattila-Evenden M E (1997) Effects of alcohol and hypnosedative drugs on digit-symbol substitution: comparison of two different computerized tests. J Psychopharmacol *11*: 313–317

Mihic S J, Qing Y, Wick M J, Koltchine V V, Krasowski M D, Finn S E, Mascia M P, Valenzuela C F, Hanson K K, Greenblatt E P, Harris R A, Harrison N L (1997) Sites of alcohol and volatile anaesthetic action on GABA$_A$ and glycine receptors. Nature *389*: 385–389

Mumenthaler M S, Taylor J L, O'Hara R, Yesavage J A (1999) Gender differences in moderate drinking effects Alcohol Res Health *23*: 55–64

Ranney T A (1994) Models of driving behavior. A review of their evolution. Accident Analy Prevention *26*: 733–750

Roache J D, Cherek D R, Bennett R H, Schenkler J C, Cowan K A (1993a) Differential effects of triazolam and ethanol on awareness, memory and psychomotor impairment. J Clin Psychopharmacol *13*: 3–15

Roache J D, Spiga R, Burt D B (1993b) Triazolam and ethanol effects on human matching-to-sample performance vary as a function of pattern size and discriminability. Drug Alcohol Depend *32*: 219

Robertson M D, Drummer O H (1994) Responsibility analysis: A methodology to study the effects of drugs in driving. Accident Analysis Prevent *26*: 243–247

Schouten J F, Bekker J A M (1967) Reaction time and accuracy. Acta Psychologica *27*: 143–153

Sternberg S (1975) Memory scanning: new findings and current controversies. Quarterly J Exp Psychol *27*: 1–32

Tiplady B, Faineteau H, Loganathan A, Spiegelberg M, Taylor Z, Wright P (1998) Effects of ethanol and temazepam on performance in memory and psychomotor tasks: a dose–response comparison. Hum Psychopharmacol *13*: 285–291

Tiplady B, Harding C, McLean D, Ortner C, Porter K, Wright P (1999) Effects of ethanol and temazepam on episodic and semantic memory: a dose–response comparison. Hum Psychopharmacol *14*: 263–269

Tiplady B, Wright P, Sinclair W, Hendry J, Gray E, Cameron E, Drummond G B (2001) Ethanol, errors, and the speed-accuracy trade-off. Pharmacol Biochem Behav *69*: 635–641

Wallgren H, Barry H I (1970) Actions of alcohol. Elsevier, New York

Wang M-Y, Rampil I J, Kendig J J (1999) Ethanol directly depresses AMPA and NMDA glutamate currents in spinal cord motor neurons independent of actions on GABA$_A$ or glycine receptors. J Pharmacol Exp Therap *290*: 362–367

Wechsler D (1958) The measurement and appraisal of human intelligence, 4th edn. Williams and Wilkins, Baltimore

Welford A T (1980) Choice reaction time: basic concepts. In Welford A T (ed.), Reaction times, pp. 73–128. Academic Press, London

Wesnes K, Warburton D M (1983) Effects of smoking on rapid visual information processing performance. Neuropsychobiology *9*: 223–229

West R, Wilding J, French D, Kemp R, Irving A (1993) Effect of low and moderate doses of alcohol on driving hazard perception latency and driving speed. Addiction *88*: 527–532

Williams E J (1949) Experimental designs balanced for the estimation of residual effects of treatments. Aust J Sci Res *2*: 149–168