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An evaluation of possible interactions between ethanol and trazodone or amitriptyline

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1 The pharmacodynamic effects of single doses of trazodone (100 mg), amitriptyline (50 mg) or placebo either alone or with ethanol (0.5 ml/kg) were investigated in six healthy volunteers in a double-blind crossover study. Plasma concentrations of the drugs and ethanol were also measured.
2 Pharmacodynamic tests were critical flicker fusion frequency threshold (CFF), choice reaction time (CRT), manual dexterity, a digit span test and visual analogue scales.
3 Blood ethanol concentrations were not influenced by the co-administration of either antidepressant.
4 t_{max} for trazodone was prolonged by ethanol but the other pharmacokinetic parameters for trazodone and amitriptyline were not influenced by ethanol.
5 Trazodone and amitriptyline caused the expected profound depressant effects on CFF, CRT, manual dexterity and on the rating scales for drowsiness, 'clear-headedness', aggression and disinhibition.
6 Ethanol alone impaired manual dexterity, increased drowsiness, reduced 'clear headedness' and also tended to reduce feelings of aggression.
7 In combination with either trazodone or amitriptyline, ethanol caused little additional effect except in the case of manual dexterity which was further impaired. This result may reflect the profound effects of the antidepressants alone and does not suggest that it is safe for patients receiving antidepressant medication to take ethanolic drinks.

Keywords trazodone amitriptyline ethanol ethanol interactions

Introduction

Alcoholic drinks, even in modest quantities, are widely believed to worsen the adverse effects of antidepressant drugs on alertness and psychomotor performance. There is evidence that this is so in the case of amitriptyline (Landauer *et al.*, 1969; Patman *et al.*, 1969; Seppälä *et al.*, 1975; Seppälä, 1977), doxepin (Seppälä *et al.*, 1975) and mianserin (Seppälä, 1977) but not for chlorimipramine, nortriptyline (Seppälä *et al.*, 1975), nomifensine (Taeuber, 1977) or zimelidine (Scott *et al.*, 1982).

Trazodone is an antidepressant agent with a chemical structure unrelated to existing psychomotor drugs (Al-Yassiri *et al.*, 1981; Brogden *et al.*, 1981; Ayd & Settle, 1982; Georgotas *et al.*, 1982; Rawls, 1982) which is sedative and impairs critical flicker fusion threshold in young and elderly volunteers (Bayer *et al.*, 1983).

The present study was designed to examine the pharmacodynamic effect and pharmacokinetics of trazodone in comparison to a standard sedative antidepressant, amitriptyline (Hindmarch,. 1980), alone or in combination with a 'social dose' of ethanol to assess possible interactions between the agents.

Methods

Study design

The study was a double-blind partially balanced crossover comparing single doses of trazodone, amitriptyline and placebo, with or without ethanol ingestion.

Preparations

Matched capsules of trazodone (100 mg), amitriptyline (50 mg) or placebo were taken in conjunction with both 0.5 ml/kg ethanol in 540 ml Barbican (non-alcoholic) beer or with Barbican beer alone. The six treatments were administered at 09.00 to 09.30 h, 2 h after a light breakfast, separated by periods of not less than 1 week, in accordance with a partially balanced Latin square schedule. Caffeinated drinks were not allowed from 22.00 h the evening before each study day until completion of the assessments while alcoholic drinks were not allowed from 24 h before until 24 h after medication.

Subjects

Six healthy non-smoking volunteers (two males; four females) aged 19–22 years weighing 61–82 kg entered the study after its purpose had been explained to them and written informed consent obtained. They were cautioned not to drive motor vehicles or operate machinery for the duration of the experimental sessions. The protocol for the study was approved by an independent Ethical Committee.

Subjects were excluded if they had taken ethanol within 24 h before the study, if they were taking other psychoactive medication or if they had a known intolerance to ethanol or psychoactive medication. They were not suffering from a current psychiatric illness and did not have a history of significant cardiac, renal, hepatic, gastric or haematological disorder. The subjects were not on a high fat diet or receiving any medication known to induce or inhibit liver enzymes, and they reported not to be drinking in excess of 15 pints of beer or 2 bottles of sherry or 3½ bottles of wine or 1 bottle of spirits per week (cf British Medical Journal 1978).

All female subjects were screened for pregnancy and were excluded if the test result was positive.

Tests used

Following a pre-experimental training session each subject was assessed under standardised conditions just before and 45, 90, 150 and 240 min after medication. The tests used were:

(a) *Critical flicker fusion frequency threshold (CFF) test* CFF (Hindmarch, 1980) was measured using the Leeds Psychomotor Tester. Threshold frequency was taken as the mean of four ascending and four descending readings. All measurements were carried out at a viewing distance of 1 metre in a small room with constant subdued artificial lighting, after allowing sufficient time for subjects to adapt to the light.

(b) *Choice reaction time (CRT)* Total CRT (Hindmarch, 1980) was also measured using the Leeds Psychomotor Tester. The CRT was taken as the mean of 30 stimulus presentations.

(c) *Digit span memory* Digit span memory was tested using a procedure similar to that in the Wechsler Adult Intelligence Scale. The subject was asked to repeat numbers consisting of an increasing number of digits immediately after verbal presentation. The number of digits was increased by one if two numbers of the same length were recalled correctly. When an error was made, the number of digits was reduced by one. The final score was taken as the number of digits in the pair recalled successfully at the second attempt at that level. The same procedure was then performed with the subjects repeating another series of numbers backwards.

(d) *Manual dexterity test* Manual dexterity was assessed by measuring the time taken for the subject seated on a chair to pick up from a tin lid (diameter 76 mm) 50 air gun pellets (diameter 5.6 mm) one at a time and drop them down a glass tube of 6 mm bore. Results were recorded as pellets/min.

(e) *Visual analogue self-rating scales* The subjects were asked to rate their current feelings by marking the appropriate place on a 100 mm line for the following four dimensions:

	Left hand extreme (0)	*Right hand extreme (100)*
1.	I can hardly keep awake.	I am as awake as I have ever been.
2.	I feel muzzy headed.	I feel clearheaded.

3.	I feel very placid.	I feel intensely violent urges.
4.	I am in full control of myself.	I feel completely lacking in inhibition.

The dimensions were designed to assess:
1. Drowsiness.
2. Clearheadedness.
3. Aggression.
4. Disinhibition.

(f) *Blood ethanol concentrations* Blood ethanol concentrations were measured by gas-liquid chromatography before and at 40, 80 and 120 min and 4, 6 and 8 h after the test treatments.

(g) *Plasma trazodone and amitriptyline concentration* Not less than 5 ml of plasma was stored at −20°C within 1 h of collection before and at 40, 80 and 120 min and at 3, 6, 8, 10, 24, 30 and 48 h after the test treatments.

Plasma trazodone was assayed using a reverse phase h.p.l.c./GC method (Ankier *et al.*, 1981) while plasma amitriptyline was assayed by the method of Thoma *et al.* (1979).

Statistical analysis

Since the observed departures from scheduled blood sampling times were negligible the scheduled times were used in the analysis for ease of presentation. The plasma trazodone and plasma amitriptyline concentrations at each sampling time and for each active treatment were averaged for the derivation of mean plasma concentration time curves for each active treatment.

For each of the 24 individual plasma time curves (i.e. six volunteers × four active medications) four parameters have been derived as follows:-

(a) AUC_{0-24}, the area under the plasma concentration time curve to 24 h. This was calculated using the trapezoidal rule,
(b) C_{max}, the maximum observed plasma concentration,
(c) t_{max}, the scheduled sampling time at which C_{max} occurred. Where C_{max} was observed at more than one time, t_{max} was taken as the arithmetic mean of the corresponding times,
(d) $t_{½}$, the elimination half-life.

AUC, C_{max} and $t_{½}$ were analysed using analysis of variance. The fitted linear model comprised the effects for treatment, ethanol and patients.

Differences in t_{max} between the treatments were examined by the distribution-free Friedman rank sum test. Particular treatment contrasts were assessed using a multiple comparison method based on the Friedman rank sum tests.

Similar analyses were carried out on all the psychomotor response variables. For each variable analysis of covariance was used with main effects for treatment, ethanol, patients, 2-way interactions for treatment × ethanol, treatment × patients and ethanol × patients and the value of the response variable at 0 min as covariate. Separate analyses of covariance were performed for each time point after drug administration at which measurements were recorded (i.e. 45, 90, 150 and 240 min). When the treatment effect was statistically significant, differences between pairs of treatments were tested using least square means and their standard errors.

Statistical analysis was carried out using the General Linear Model procedure of the Statistical Analysis System.

Results

Critical flicker fusion frequency threshold (CFF; Figure 1)

Trazodone increased CFF at 45 min compared with placebo and amitriptyline ($P < 0.01$); thereafter trazodone and amitriptyline did not differ from each other, but both drugs increased CFF significantly compared with placebo at all times ($P < 0.01$).

There was no statistically significant additional effect of ethanol on any treatment.

Total choice reaction time (CRT; Figure 2)

Trazodone increased CRT at 45 min compared with amitriptyline ($P < 0.01$) but there were no other significant differences between treatments. There was an overall effect of ethanol alone at 150 min ($P = 0.05$) but the interaction between ethanol and any one treatment was not statistically significant ($P = 0.72$). There was a trend for both active treatments to prolong CRT compared to placebo.

Manual dexterity (Figure 3)

Trazodone impaired manual dexterity at 45 min compared with placebo ($P = 0.02$). At 150 min, both trazodone and amitriptyline reduced manual dexterity compared with placebo ($P < 0.01$), but they did not differ from each other. Ethanol appeared to impair manual dexterity

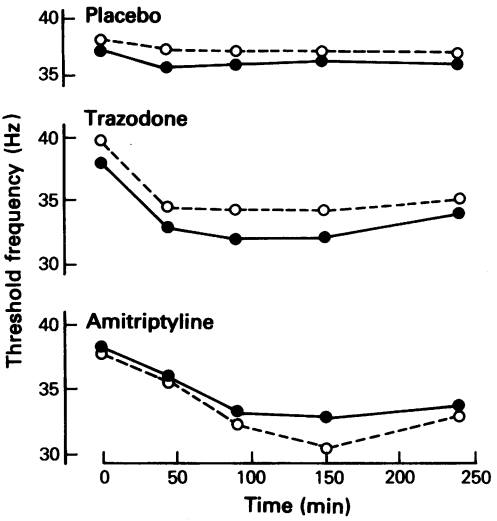

Figure 1 Critical flicker fusion (○ without ethanol, ● with ethanol).

after all treatments, but this was only statistically significant at 150 min ($P = 0.01$).

Digit span (Table 1)

There was no effect of any treatment on digit repetition 'forwards'. Amitriptyline impaired digit repetition 'backwards' at 150 min ($P < 0.01$); trazodone and ethanol had no statistically significant effect at any time.

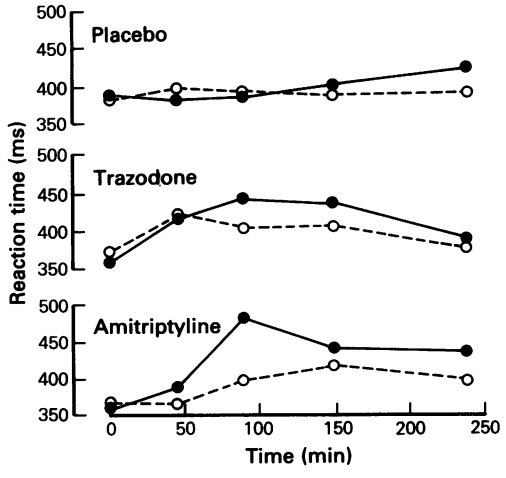

Figure 2 Choice reaction time (○ without ethanol, ● with ethanol).

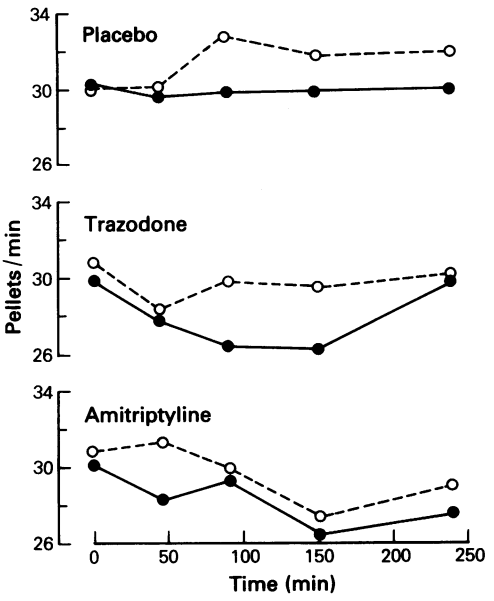

Figure 3 Manual dexterity (○ without ethanol, ● with ethanol).

Visual analogue scales

(a) *Drowsiness (Figure 4)* The scores for trazodone and amitriptyline were significantly different from placebo indicating more drowsiness at all times ($P < 0.01$) in all treatment comparisons except trazodone *vs* placebo at 240 min) ($P > 0.05$).

Amitriptyline was significantly more sedative than trazodone at 150 min ($P < 0.01$) and 240 min ($P < 0.05$). Ethanol generally increased drowsiness compared with ethanol-placebo, but an overall statistical significance was reached only at 150 min ($P = 0.03$). There was no obvious additional effect of ethanol upon the sedation caused by the active drugs.

(b) *Clearheadedness (Figure 5)* The scores for trazodone and amitriptyline alone were significantly different from placebo indicating a reduction in clearheadedness at all times up to 150 min ($P < 0.01$). For amitriptyline there was also a significant effect at 240 min ($P < 0.01$) at which time the subjects receiving trazodone were significantly more clearheaded than those receiving amitriptyline ($P < 0.05$). At 45 min, trazodone had a greater effect than amitriptyline ($P < 0.01$).

Ethanol alone tended to reduce clearheadedness at all times after administration,

Table 1 Digit span score, mean number of digits recalled correctly

Time (min)		*Trazodone*		*Amitriptyline*		*Placebo*	
		Without ethanol	*With ethanol*	*Without ethanol*	*With ethanol*	*Without ethanol*	*With ethanol*
Forward	0	7.0	6.7	6.8	7.3	7.0	7.8
	45	6.8	7.7	7.3	7.0	7.3	7.5
	90	7.4*	7.5	7.7	6.8	7.8	7.3
	150	7.3	7.2	7.2	7.0	7.7	7.5
	240	7.0	7.5	7.7	7.3	7.8	7.3
Backward	0	5.7	5.6	6.2	5.7	5.2	6.0
	45	5.8	5.3	6.0	5.7	5.5	5.5
	90	5.8*	6.2	5.5	5.8	5.2	6.2
	150	5.5	5.3	4.3	5.0	6.3	6.2
	240	6.0	5.5	5.5	5.5	6.2	5.8

* Means based on five subjects since sixth subject unable to complete task because of sedation.

but this effect was only statistically significant at 45 min ($P = 0.01$). In contrast with the reduction in clearheadedness when ethanol was given with placebo there was no obvious additional effect of ethanol with either trazodone or amitriptyline.

(c) *Aggression (Figure 6)* There was a tendency for both drugs to cause a reduction in aggression but this effect was only significant at 150 min for amitriptyline compared with placebo ($P < 0.01$). Ethanol exerted no statistically significant separate or additional effects.

(d) *Disinhibition (Figure 7)* Trazodone and amitriptyline differed significantly from placebo at all times up to 150 min ($P < 0.01$); however, at 240 min only amitriptyline differed from placebo ($P < 0.01$) while amitriptyline and trazodone were significantly different from each other ($P < 0.05$).

Blood ethanol concentrations (Figure 8)

There was no significant difference between treatments in respect of blood ethanol concentrations.

The median time to observed peak of blood ethanol concentration was 40 min after ami-

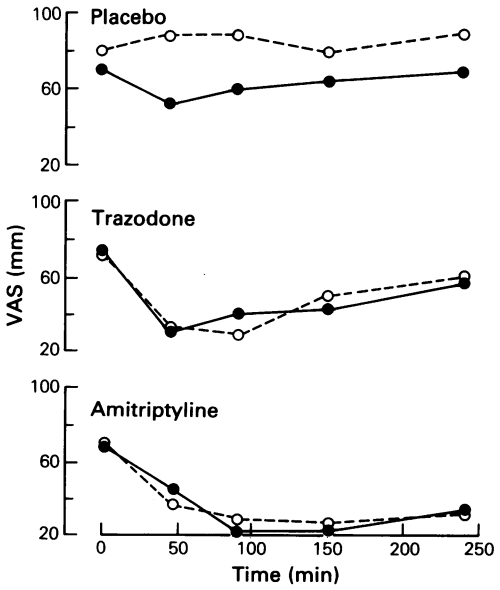

Figure 4 Visual analogue scale for drowsiness (○ without ethanol, ● with ethanol). 0 = I can hardly keep awake. 100 = I am as awake as have ever been.

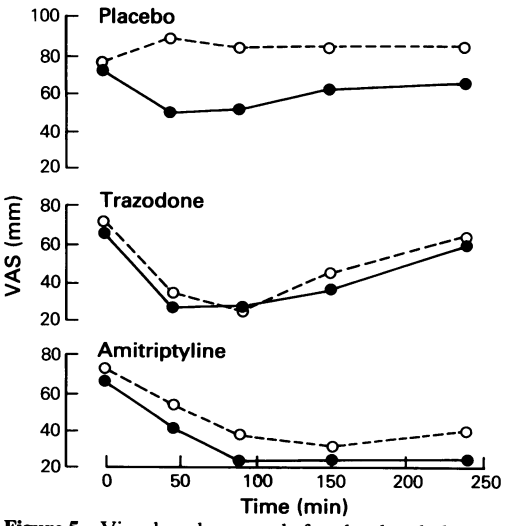

Figure 5 Visual analogue scale for clearheadedness (○ without ethanol, ● with ethanol). 0 = I feel muzzy-headed. 100 = I feel clear-headed.

Table 2 Results of analysis of co-variance by repeated measures, applied to psychometric tests

Psychometric variable	*Statistical significance (P value)*		*Least square means, ranked in order of magnitude of effect:*		
	Treatment	*Alcohol*	*Most effect* ⟷		*Least effect*
Critical flicker fusion	0.005	0.80	Traz	Ami	Plac
Choice reaction time	0.75	0.22	Ami	Traz	Plac
Manual dexterity	0.02	0.06	Traz	Ami	Plac
Drowsiness	0.0003	0.49	Ami	Traz	Plac
Clearheadedness	0.0001	0.03	Ami	Traz	Plac
Aggression	0.03	0.89	Ami	Traz	Plac
Disinhibition	0.08	0.5	Ami	Traz	Plac

Ami = Amitriptyline; Traz = Trazodone; Plac = Placebo
Values underscored by a common line are not significantly different from each other at the 5% level.

triptyline and 80 min after placebo or trazodone. No ethanol was detectable in blood after 240 min.

Pharmacokinetics of amitriptyline and trazodone

Table 3 shows mean plasma concentrations of trazodone and amitriptyline with and without ethanol. Tables 3 and 4 show the pharmacokinetic parameters for the two drugs under both conditions.

There was no significant difference in mean concentrations of trazodone or amitriptyline with or without ethanol (Table 3).

Amitriptyline kinetics showed marked variability within and between subjects. C_{max} showed no significant difference between mean values obtained with and without ethanol for either treatment (Table 4). t_{max} for trazodone

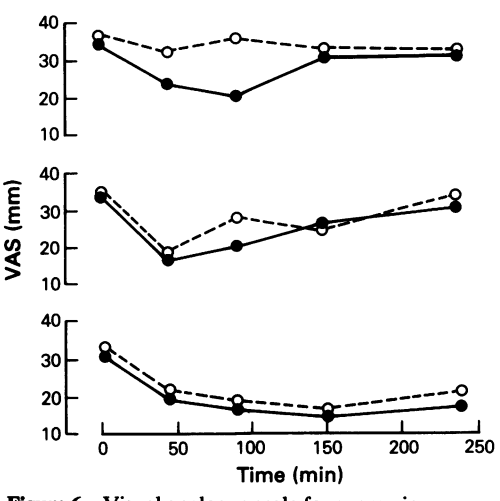

Figure 6 Visual analogue scale for aggression (○ without ethanol, ● with ethanol). 0 = I feel very placid. 100 = I feel intensely violent urges.

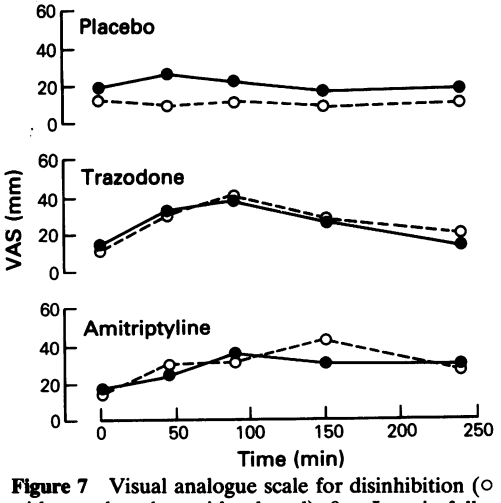

Figure 7 Visual analogue scale for disinhibition (○ without ethanol, ● with ethanol). 0 = I am in full control of myself. 100 = I feel completely lacking in inhibition.

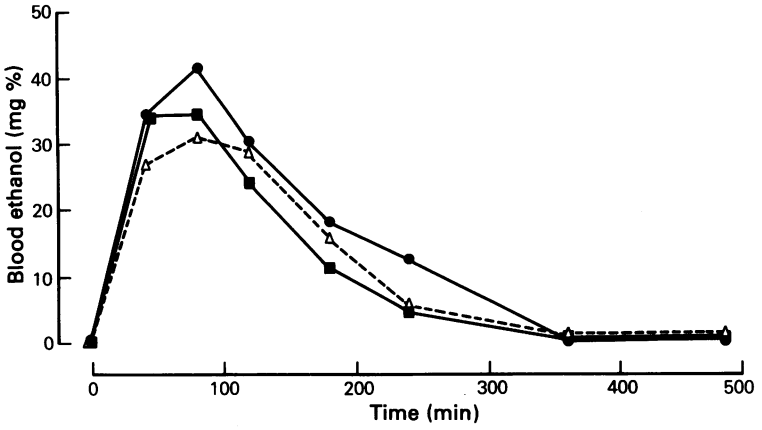

Figure 8 Mean blood ethanol, ●——● with trazodone, ■——■ with amitriptyline, △-----△ with placebo.

was significantly prolonged by ethanol administration ($P = 0.031$) whereas t_{max} for amitriptyline was shortened in two and unchanged in four subjects. For both drugs, neither AUC_{0-24} nor $t_{½}$ was significantly prolonged by ethanol. The $t_{½}$ could not be calculated for amitriptyline in four instances, either because in some cases the half-life was short and the sampling times too widely spaced, or because in others the half-life was too long.

Discussion

Compared with placebo, both trazodone and amitriptyline were statistically different indicating impairment of CFF, CRT and manual dexterity. On the visual analogue scales, both trazodone and amitriptyline increased drowsiness, reduced 'clearheadedness' and tended to reduce feelings of aggression and inhibition. These effects were generally similar in intensity for the two active drugs at the doses chosen, which are clinically relevant. The only obvious difference between the drugs was that the effect of trazodone occurred earlier and was less persistent. These results are entirely consistent with the known sedative effects of these antidepressants.

Ethanol alone impaired manual dexterity, increased drowsiness, reduced 'clearheadedness' and also tended to reduce feelings of aggression. These modest effects were present with mean circulating ethanol concentrations which did not exceed 30 mg%.

In combination with either trazodone or amitriptyline, ethanol caused a greater impairment of manual dexterity than was seen with trazodone or amitriptyline alone. There were

Table 3 Mean plasma concentrations of trazodone and amitriptyline

	Trazodone (μg/ml)		*Amitriptyline (ng/ml)*	
Time (h)	*Without ethanol*	*With ethanol*	*Without ethanol*	*With ethanol*
0	0	0	0	0
2/3	1.15	0.71	0	1.0
4/3	1.37	1.27	3.3	5.8
2	1.27	1.42	12.7	9.5
3	1.09	1.12	11.0	12.0
6	0.56	0.61	11.2	8.7
8	0.37	0.40	9.3	6.8
10	0.27	0.27	9.0	3.7
24	0.03	0.04	4.0	1.4
30	0.02	0.02	1.0	0.8
40	0	0	0	0.8

Table 4 Some pharmacokinetic parameters for trazodone and amitriptyline with or without ethanol

Subject	Trazodone								Amitriptyline							
	C_{max} (μg/ml)		t_{max} (min)		AUC_{24} (μg ml^{-1} h)		$t_{½}$ (h)		C_{max} (ng/ml)		t_{max} (min)		AUC_{24} (ng ml^{-1} h)		$t_{½}$ (h)	
	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B
1	1.63	1.63	80	120	7.68	9.26	2.84	2.51	16.0	14.0	480	150	169	146	–	5.2
2	1.40	1.56	80	120	9.04	9.99	4.30	4.53	10.0	10.0	180	180	111	45	11.0	–
3	1.87	1.56	40	80	6.16	6.98	3.19	2.73	6.0	10.0	270	150	31	116	–	4.7
4	1.81	0.83	120	180	11.16	4.36	4.39	2.71	37.0	14.0	120	120	346	60	12.6	4.8
5	1.77	2.36	40	80	12.18	12.87	7.34	5.52	14.0	8.0	180	180	246	31	45.9	–
6	1.50	1.67	80	120	10.42	12.99	3.84	5.09	17.0	20.0	180	180	230	260	15.3	25.0
Mean	1.66	1.60	73.3	116.7	9.44	9.41	4.32	3.85	16.7	12.7	235.0	160.0	188.7	109.3	–	–

A = without ethanol, B = with ethanol

no other interactions between ethanol and either antidepressant.

Blood ethanol concentrations were not influenced by either trazodone or amitriptyline. The observed C_{max} was about half the UK legal limit for driving a motor vehicle of 80 mg%. These concentrations are about what might be expected from a dose of ethanol equivalent to a 'social' drink of about 2 pints of beer or two double measures of spirits. The observed pharmacokinetic parameters for trazodone and amitriptyline are similar to those described previously (Ankier *et al.*, 1981; Bayer *et al.*, 1983; Jorgensen & Staer, 1976). Ethanol administration did not modify these except in the case of t_{max} for trazodone which was prolonged perhaps due to an ethanol-induced delay in gastric emptying. In the case of amitriptyline, t_{max} was much longer than for trazodone making it less susceptible to such an effect.

The results of this acute study show that the pharmacodynamic effects of a clinically relevant dose of trazodone or amitriptyline were not generally exacerbated by a 'social' dose of ethanol. However, it may well be that the effects of trazodone or amitriptyline alone were so profound that any additional effect of ethanol could not be detected. We do not suggest, therefore, that it is safe for patients receiving antidepressant medication to take ethanolic drinks.

Although there are no previous studies reported which are directly comparable with the present one, our results are broadly compatible with the findings of Seppälä *et al.* (1975) and Seppälä (1977). These workers used lower doses of amitriptyline but the subjects were studied during 2 weeks of treatment. Patients tend to become tolerant to the sedative effects of drugs during chronic treatment, and it could be argued that the adverse effects of ethanol on psychomotor performance might be more serious and more easily detected when examined on a background of only minor drug-related sedation. In fact, the available evidence suggests that the impairment of performance by both antidepressant and ethanol diminishes during the course of a few weeks' treatment with the drugs (Patman *et al.*, 1969; Seppälä *et al.*, 1975; Seppälä, 1977).

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