

KINETIC AND DYNAMIC INTERACTION OF CLOBAZAM AND ALCOHOL

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- 1 The present study was designed to investigate both pharmacodynamic and pharmacokinetic interactions of clobazam and alcohol.
- 2 Eight healthy male volunteers participated in an intraindividual Latin square comparison of (a) clobazam 20 mg; (b) placebo; (c) alcohol + placebo; and (d) alcohol + clobazam 20 mg. Alcohol was administered orally in quantities individually calculated to yield serum alcohol concentrations of about 1000 µg/ml. The comparison of treatments (a) against (b) and (c) against (d) was double blind. Drug-free periods between the trials were 7 days.
- 3 Pharmacodynamic assessments were carried out before and 2, 3 and 5 h after administration using a series of tests of choice reaction performance, simple reaction time, two-hand coordination and body sway, together with self ratings, side-effects lists, vital signs and blood chemistry.
- 4 Blood samples were obtained before and 50, 100, 160, 220, 280, 340 and 1440 min after administration. Serum levels of clobazam and alcohol were determined by gas chromatography.
- 5 The dynamic results show significant differences between the alcohol and non-alcohol treatments and no significant difference either between clobazam and placebo, or between alcohol alone and alcohol + clobazam. Numerically, however, the detrimental effects of the combination were consistently stronger, indicating a possible pharmacodynamic interaction.
- 6 A pharmacokinetic interaction was found, as the serum clobazam levels were higher after combined administration of clobazam and alcohol than after clobazam alone. An enhanced absorption of clobazam and a reduced distribution volume may explain this finding which is comparable to findings obtained with diazepam and alcohol (Hayes *et al.*, 1977).
- 7 It is concluded that combined ingestion of clobazam and alcohol is likely to be more hazardous than that of alcohol alone.

Introduction

ALCOHOL is known to have detrimental effects on cognitive and psychomotor performance (Evans *et al.*, 1974). Many benzodiazepines have similar effects (Linnoila, 1973), although the ratio of doses improving anxiety to doses impairing performance seems to vary from potent sleep-inducing benzodiazepines (for example, flunitrazepam) to compounds like clobazam, which seems to be non-sedative at therapeutic doses. There is vast evidence that interactions occur between alcohol and benzodiazepines (Linnoila & Mattila, 1973) due to a synergism of their pharmacodynamic effects and/or due to an increased bioavailability of the benzodiazepine when administered with alcohol (Hayes *et al.*, 1977).

The relevance of these interactions for the treatment of outpatients is widely recognized.

Studies of clobazam and alcohol by Berry *et al.* (1974) have indicated that the detrimental effects of the

combination are stronger than those of alcohol alone. The actual blood alcohol concentrations, however, were comparatively low (about 250 µg/ml) in the first experiment and so high (about 1200 µg/ml) in the second one that some subjects were unable to perform tests. Also, the dose of clobazam (10 mg) was comparatively low.

The present study was undertaken to investigate interactions of intermediate blood alcohol concentrations and sufficiently high clobazam doses. Furthermore, possible pharmacokinetic interactions of both agents have been investigated.

Methods

Preparations

Clobazam tablets (each 20 mg) and matching placebos were used. Alcohol was administered in the

form of beer and brandy which was found to be the most tolerable presentation with the subject sample used in this study.

All subjects drank 1000 ml beer (about 38.2 g alcohol) and 129.25 ± 27.74 ($\bar{X} \pm s.d.$) ml brandy (about 39.03 ± 8.38 g alcohol) individually calculated according to body weight. The administered alcohol quantities were calculated to produce maximum serum alcohol concentrations of about 1000 $\mu\text{g/ml}$. The drinks were administered in portions equally distributed over a drinking period of 90 minutes.

Subjects

Eight healthy male subjects whose main characteristics are shown in Table 1 were selected, the

Table 1 Characteristics of subjects

Variable	Dimension	Mean	s.d.
Age	Years	39.38	3.42
Height	Centimetres	177	7.10
Weight	Kilograms	77.26	8.30
Neuroticism	MPI N score	20.63	9.09
Extraversion	MPI E score	23.75	7.83

main selection principles being their moderate drinking habits and elevated Maudsley Personality Inventory (MPI) scores. All subjects were thoroughly informed about the protocol of the study and gave their written informed consent.

They underwent physical and laboratory examinations before and after the study. On trial days driving motor cars was not permitted and the subjects were transported by taxi.

Pharmacodynamic assessments

Figure 1 shows the time schedule used on each trial day. At each of the assessment periods indicated a series of pharmacodynamic assessments was carried out as shown in Table 2. These assessments consisted of tests of choice reaction performance, reaction time, two-hand coordination and body sway, visual analogue self-rating scales, a side-effect list, and measurements of heart rate, blood pressure (supine) and some safety parameters.

Figure 1 Time schedule

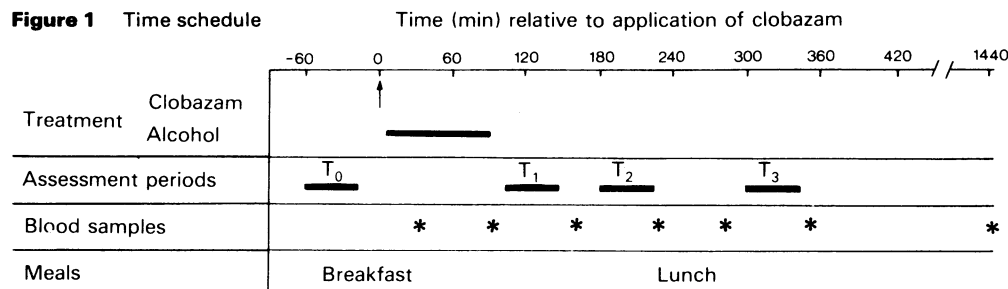


Table 2 Pharmacodynamic assessments

Type	Assessments
Behavioural	Choice reaction task, 525 stimuli Simple reaction task, visual stimuli Two-hand coordination (tracking) Body sway, computerized
Subjective	100 mm visual analogue scales Depressive – euphoric Active – inactive Tired – alert Relaxed – tense Anxious – calm
Safety	Side-effect check list Heart rate, supine Blood pressure, supine Blood chemistry

As the results of some of the tests used may be subject to training effects, all subjects were individually trained in these tests until no further increase in performance could be obtained and were then admitted to the trial itself.

The performance variables were recorded in an on-line computer setting and have been described elsewhere (Taeuber, 1977).

As a new measurement we developed a computer on-line analysis of body sway in Romberg's test. Body movements were automatically analyzed for the power spectrum using the Fast Fourier Transformation. The amplitudes were classified and plotted in a histogram. The mean frequency and mean amplitude were used as variables. Figure 2 shows a block diagram of this method (Sittig & Taeuber, in preparation).

Pharmacokinetic assessments

For the investigation of clobazam and alcohol kinetics and of potential pharmacokinetic interactions, blood samples were obtained before administration and 50, 100, 160, 220, 280, 340 and 1440 min after administration of clobazam (Figure 1).

Plasma levels of both clobazam and alcohol were determined from randomized samples using gas chromatography. The gas chromatography assay for clobazam is described elsewhere (Hadju, P., Uihlein, M., & Damm, D., in preparation).

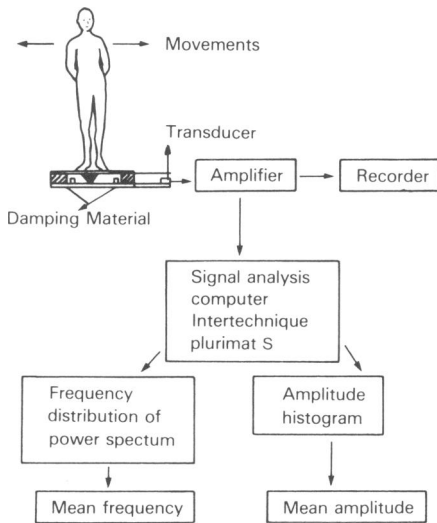


Figure 2 Block diagram of frequency and amplitude analysis of body sway.

Experimental design

The trial was carried out as an intraindividual comparison of the following acute treatments: (a) clobazam 20 mg + mineral water; (b) clobazam placebo + mineral water; (c) alcohol + clobazam 20 mg; (d) alcohol + clobazam placebo. The intraindividual sequence of these treatments was varied according to the Latin square design. Drug-free intervals between the treatments were 7 days. Due to the lack of a true alcohol placebo, only the comparisons of treatments (a) against (b) and (c) against (d) were carried out double blind.

The performance variables were analyzed using factorial analysis of variance for the Latin square model (Winer, 1971).

The results of the 100 mm scales and the pharmacokinetic parameters were compared using the randomization test for matched pairs (Siegel, 1956).

Results

Pharmacodynamics

All performance tests and the computerized body sway (Romberg test) yielded consistent significant treatment effects. These were exclusively related to differences between alcohol and non-alcohol conditions. No significant differences were found between clobazam and placebo or between alcohol alone and alcohol + clobazam. A summary of these findings is given in Tables 3–5. No significant differences were found before administration.

Figures 3–8 show findings obtained with the choice

reaction test, simple reaction time, two-hand coordination and body sway.

Although there were no significant differences between alcohol alone and alcohol + clobazam, Figures 3, 5, 7 and 8 show that the detrimental effects of the combination tended to be stronger than those of

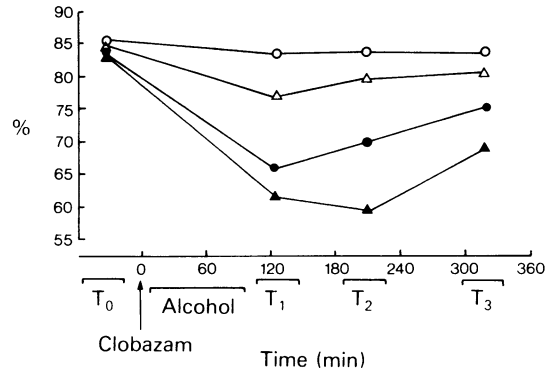


Figure 3 Choice reaction task: percentage of correct responses. Means of eight subjects; Latin square design. O, placebo; Δ, clobazam, 20 mg; ●, alcohol; ▲, clobazam, 20 mg and alcohol.

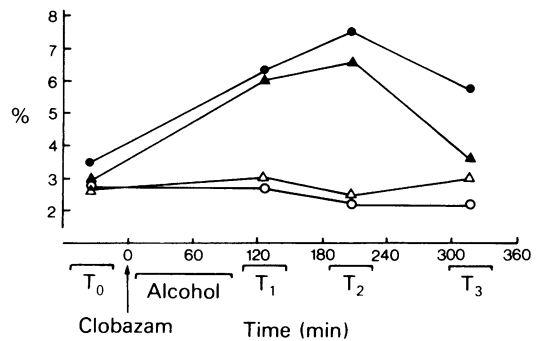


Figure 4 Choice reaction task: percentage of mistakes. Means of eight subjects; Latin square design. O, Placebo; Δ, clobazam, 20 mg; ●, alcohol; ▲, clobazam, 20 mg and alcohol.

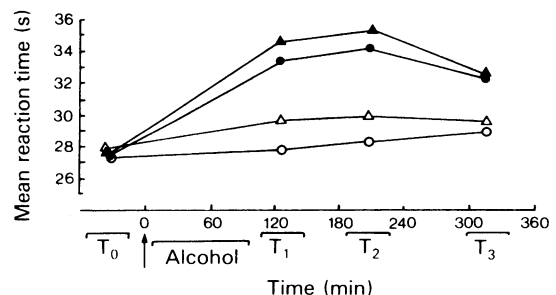


Figure 5 Simple reaction task: mean reaction time of 30 reactions. Means of eight subjects; Latin square design. O, Placebo; Δ, clobazam, 20 mg; ●, alcohol; ▲, clobazam, 20 mg and alcohol.

Table 3 Comparison of treatment effects 2 h after application

	1 vs 2	3 vs 4	1 vs 3	1 vs 4	2 vs 3	2 vs 4
Choice reaction						
% Correct responses			*	*		*
% Mistakes			*	*	*	*
% Delayed responses			*	*		
Simple reaction						
Mean reaction time			*	*	*	*
Two-hand coordination						
Time required						
No. of deviations			*	*	*	*
Off target time						
Body sway						
Mean amplitude			*	*	*	*
Mean frequency			*	*		

*P < 0.05.

1, Placebo; 2, clobazam; 3, alcohol + placebo; 4, alcohol + clobazam.

Table 4 Comparison of treatment effects 3 h after application

	1 vs 2	3 vs 4	1 vs 3	1 vs 4	2 vs 3	2 vs 4
Choice reaction						
% Correct responses			*	*		*
% Mistakes			*	*		*
% Delayed responses				*		*
Simple reaction						
Mean reaction time			*	*	*	*
Two-hand coordination						
Time required						
No. of deviations			*	*	*	*
Off target time						
Body sway						
Mean amplitude			*	*	*	*
Mean frequency			*	*	*	*

*P < 0.05. (1–4 as in Table 3).

Table 5 Comparison of treatment effects 5 h after application

	1 vs 2	3 vs 4	1 vs 3	1 vs 4	2 vs 3	2 vs 4
Choice reaction						
% Correct responses						
% Mistakes						
% Delayed responses						
Simple reaction						
Mean reaction time			*	*	*	*
Two-hand coordination						
Time required						
No. of deviations						
Off target time			*	*		
Body sway						
Mean amplitude				*		*
Mean frequency						

*P < 0.05. (1–4 as in Table 3).

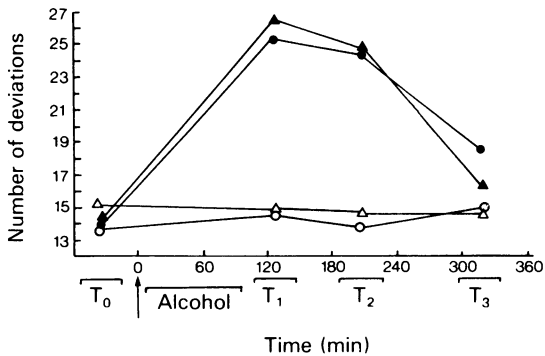


Figure 6 Two-handed coordination: number of deviations. Means of eight subjects; Latin square design. ○, Placebo; △, clobazam, 20 mg; ●, alcohol; ▲, clobazam, 20 mg and alcohol.



Figure 7 Body sway (computerised): mean amplitude of amplitude histogram. Means of eight subjects; Latin square design. ○, Placebo; △, clobazam, 20 mg; ●, alcohol; ▲, clobazam, 20 mg and alcohol.

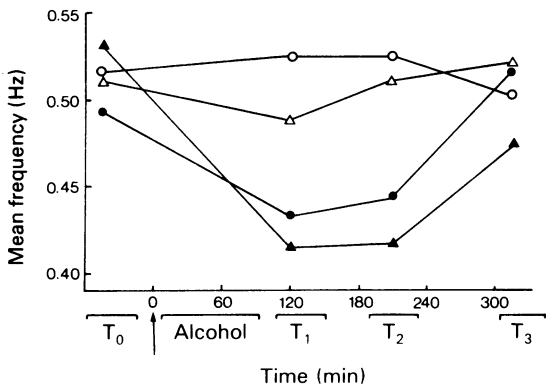


Figure 8 Body sway (computerised): mean frequency of the power spectrum (Hz). Means of eight subjects; Latin square design. ○, Placebo; △, clobazam, 20 mg; ●, alcohol; ▲, clobazam, 20 mg and alcohol.

alcohol alone. The variables 'choice reaction task/% mistakes' and 'two-hand coordination/no. of deviations' (Figures 4 and 6) do not indicate stronger effects

of the combination compared with alcohol alone. These variables, however, showed no clobazam effects.

These data, although not supported by statistical inference, may suggest that some clobazam-alcohol interaction can be seen in such variables which are altered by clobazam effects.

Neither subjective nor laboratory variables showed any significant treatment effects.

Pharmacokinetics

Figure 9 shows the serum alcohol concentration-time curves. No significant differences in alcohol kinetics

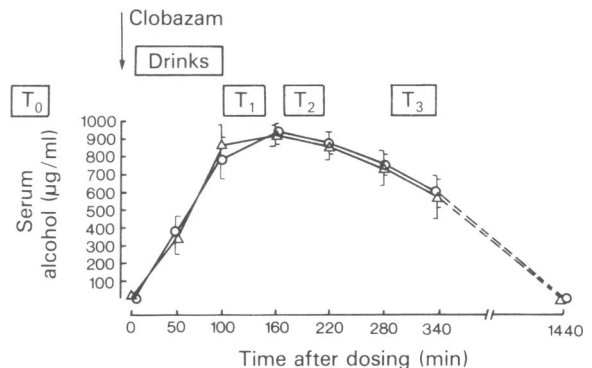


Figure 9 Mean (\pm s.e.m.) serum alcohol concentrations after alcohol alone or alcohol with clobazam in eight subjects; cross-over design. ○, Clobazam and alcohol; △, alcohol alone. T, Test series (pharmacodynamics).

were found between the administration of alcohol alone and of alcohol with clobazam. The peak serum levels of alcohol were $952.5 \pm 68.2 \mu\text{g/ml}$ after alcohol and $932.5 \pm 54.4 \mu\text{g/ml}$ after alcohol + clobazam. The areas under the curves were $228.0 \pm 12.0 \text{ mg}\cdot\text{min/ml}$ after alcohol and $232.3 \pm 12.6 \text{ mg}\cdot\text{min/ml}$ after alcohol + clobazam.

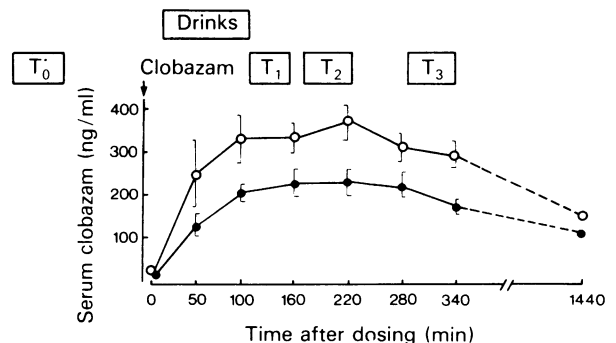


Figure 10 Mean (\pm s.e.m.) serum clobazam levels after clobazam plus alcohol or water in eight subjects. ●, Clobazam and water; ○, clobazam and alcohol. T, Test Series (pharmacodynamics).

Figure 10 shows the serum clobazam concentration–time curves. The peak serum levels after clobazam + alcohol were 388.75 ± 157.16 ng/ml and were significantly higher than after clobazam alone: 243.75 ± 86.67 ng/ml ($P > 0.05$) (Figure 11). Also, the areas under the curves differed significantly: $63.5 \pm$

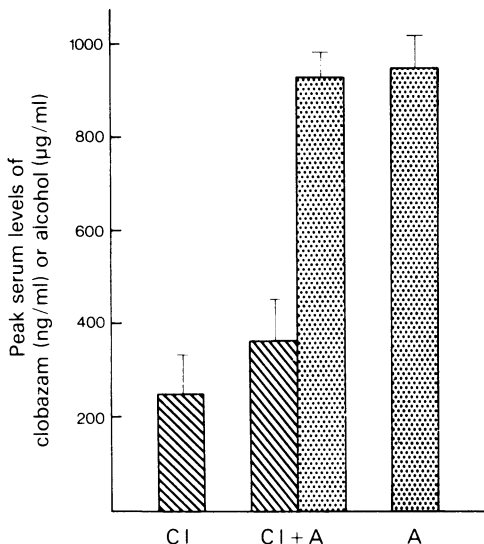


Figure 11 Peak serum levels of clobazam (CI) and alcohol (A) given alone and in combination (CI+A). Mean and s.e.m. of eight subjects; Latin square design.

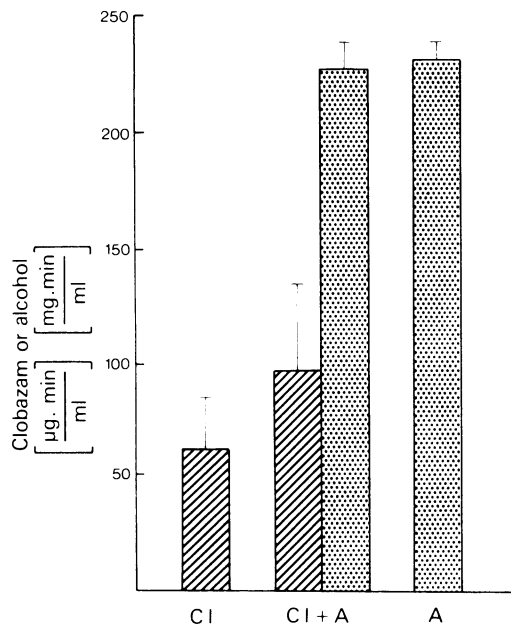


Figure 12 Areas under the serum concentration–time curves. 0–340 min after administration. Mean and s.d. of eight subjects.

24.5 µg·min/ml after clobazam alone and 98.2 µg·min/ml after clobazam + alcohol ($P > 0.05$) (Figure 12).

The elevated plasma clobazam concentrations, when clobazam was administered with alcohol, deserve an explanation. Urinary elimination of total radioactivity after oral doses of [14 C]-labelled clobazam shows that at least 80% of the dose was absorbed. Thus, an increase of the areas under the curves of about 54% (see Figure 12) cannot be explained simply by an enhanced rate of clobazam absorption. A diminished volume of distribution and/or an inhibition of metabolic biotransformation are also possible ways in which alcohol may have altered the clobazam kinetics.

Similar findings with diazepam and alcohol have been reported and discussed by Hayes *et al.* (1977).

Conclusions

Our findings demonstrate that there is a clear pharmacokinetic interaction, in that alcohol, when administered with clobazam, enhances clobazam bioavailability. On the other hand, clobazam does not alter the alcohol kinetics. The pharmacodynamic findings also illustrate this clobazam–alcohol interaction: in almost all performance variables the detrimental effects of alcohol + clobazam were stronger than those of alcohol alone. This difference, however, is not as pronounced as our pharmacokinetic data would suggest. As the clobazam levels were more than 50% elevated after administration with alcohol, one would expect the effects of this combination to be more than additive, that is, stronger than the sum of clobazam/placebo and alcohol/placebo differences. Our data seem to confirm this at the two last assessment periods in the choice reaction task (Figures 2 and 3) and in body sway amplitudes (Figure 7). These data were therefore tested for non-additivity, but this was not confirmed.

Although an essential part of our pharmacodynamic data, that is, the differences between the effects of alcohol alone and those of alcohol + clobazam, did not reach the level of statistical significance, they are quite consistent and should justify the conclusion that combined effects of clobazam and alcohol may be more hazardous than the effects of alcohol alone.

Elevated plasma levels of clobazam, when ingested with alcohol, may contribute to these hazards. The mechanism of the observed pharmacokinetic interaction deserves further clarification.

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Discussion

DR P. BERRY (Nottingham) described his own studies of the interaction of clobazam with alcohol. After clobazam 30 mg daily for 1 week, blood alcohol levels in normal volunteers following the ingestion of a standard amount of alcohol (220–295 ml whisky over 1 h) were significantly lower than before the drug. No alcohol had been allowed between the test days, and in spite of the difference in blood alcohol levels there was no difference in motor performance following the

alcohol before and after administration of clobazam. He wondered whether this result suggested that clobazam may affect the metabolism of alcohol.

DR K. TAEUBER emphasized that the single dose studies which he had reported revealed no difference in the kinetics of alcohol when administered alone or in combination with clobazam. No repeated dose studies had been carried out.