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DYNAMIC INTERACTION OF NOMIFENSINE WITH ALCOHOL

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1 Nine healthy volunteers participated in a comparative study of the effects of nomifensine, nomifensine plus alcohol, and placebo plus alcohol, on aspects of psychomotor performance.

2 The study was carried out according to a Latin square design and each treatment was separated from the preceding treatment by 7 days.

3 Placebo plus alcohol impaired performance, increased pulse rate and blood pressure, and increased feelings of activity and euphoria.

4 Nomifensine plus alcohol produced the same subjective and objective changes as placebo plus alcohol, but in no instance were changes any greater.

5 Nomifensine alone produced none of these changes.

6 It was concluded that single doses of nomifensine did not potentiate the effect of alcohol.

Introduction

Nomifensine, a tetrahydroisoquinoline compound, has been shown to be an efficient and safe antidepressant drug. In a large number of controlled trials, its effects in healthy volunteers and in various kinds of depressed patients have been investigated. Although the findings of these trials describe the pharmacodynamics of nomifensine as a monosubstance adequately, there existed a lack of information on the effects of this compound when given in combination with other psychoactive agents.

It is known from several studies (for example, Hindmarch, 1977; Wittenborn, 1976) that nomifensine does not impair mental functions such as attention, vigilance or psychomotor performance. This is felt to be a major advantage in the use of this drug in depressed out-patients. Alcohol, on the other hand, probably being the psychoactive agent which would most frequently be used at the same time as nomifensine, has detrimental effects possibly on all kinds of human performance.

It was the aim of this trial to examine the pharmacodynamic effects of alcohol, alone and in combination with nomifensine, and to analyze the findings with respect to possible interactions among both agents.

Methods

Investigational preparations

The following preparations were used. Nomifensine: three capsules of 25 mg each = 75 mg nomifensine; nomifensine–placebo: three capsules of identical appearance; alcohol: to provide for a realistic drinking situation, wine was administered in quantities individually titrated according to the subjects' body weight. Thus, an average volume of 754 ml per subject was drunk evenly distributed over a 90-min period starting 15 min after the application of nomifensine.

Subjects

This study was carried out in nine healthy volunteers the main characteristics of whom are shown in Table 1.

All subjects had been informed about the nature of the trial and had given their written informed consent. They underwent a thorough physical and laboratory examination before and after the study. On trial days the subjects were not allowed to drive motorcars and were transported by taxi.

Assessments of drug–alcohol effects

A series of tests of psychomotor performance, reaction time, attention and subjective mood state together with measurements of pulse, blood pressure and body sway, was administered before and at fixed intervals after each administration. Figure 1 shows the time schedule for each trial day. Table 2 lists all variables which were assessed at each assessment period.

To minimize interferences between drug effects and training effects, all subjects underwent two training periods: individual training for each subject in all

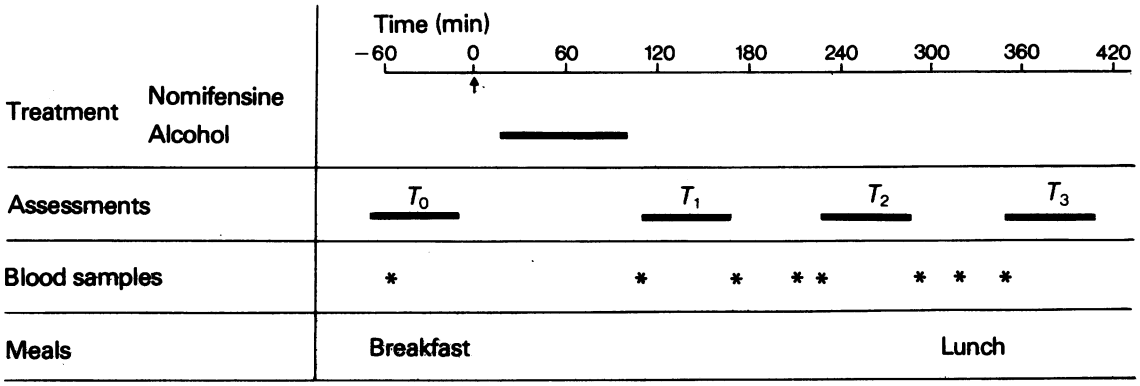

Figure 1 Time schedule for each trial day during nomifensine–alcohol interaction study

tests; collective training on a full trial day without treatment.

Experimental design

The trial was designed as an intra-individual comparison of the following acute treatments: (a) nomifensine 75 mg + mineral water; (b) nomifensine 75 mg + about 750 ml wine; (c) nomifensine-placebo + about 750 ml wine. The intra-individual sequence of these treatments was varied according to a Latin square design. Between the treatments there were 7-d intervals. Since a true alcohol-placebo was not available, only the above treatments (b) and (c) were

Table 1 Characteristics of subjects

Variable	*Dimensions*	*Arithmetic mean*	*Standard deviation*
Age	Yr	39.00	4.35
Height	cm	178.50	5.21
Body weight	kg	80.20	5.44
Neuroticism	MPI N scores	17.11	13.49

Table 2 Assessments

Type	*Assessments*
Chemical	Blood alcohol concentration Nomifensine plasma levels
Vital signs	Blood pressure (standing and supine) Heart rate (standing and supine) Modified Romberg (body sway)
Behavioural	Multiple choice reaction task Simple reaction time (acoustic stimuli) Both-handed coordination Perception threshold Cancellation test (attention)
Subjective	100 mm visual analogue scales for: Depressive – euphoric Active – passive Tired – alert Relaxed – tense Anxious – calm Side-effect list

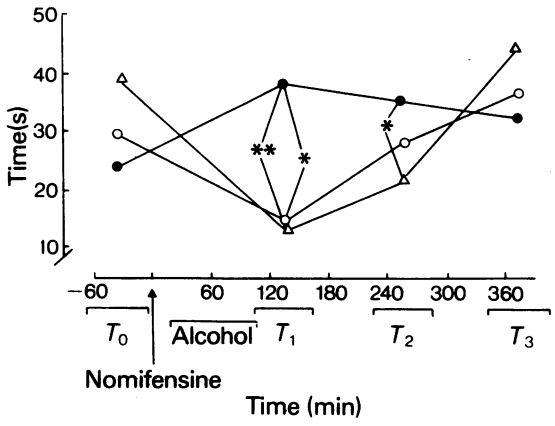

Figure 2 Modified Romberg test. Time subject is able to maintain posture. •, Nomifensine; ○, alcohol; △, nomifensine plus alcohol. $*P < 0.05$; $**P < 0.01$.

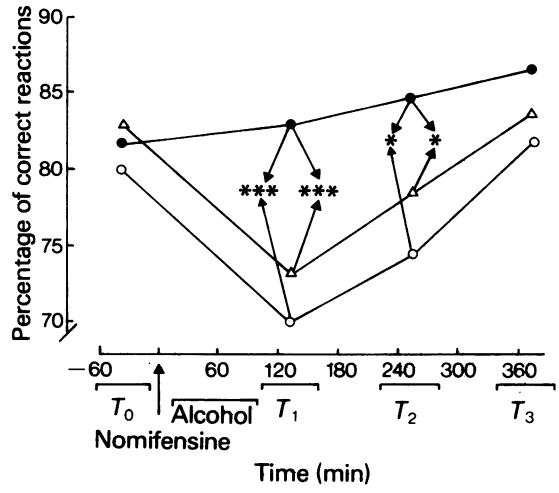

Figure 3 Multiple choice reaction task. Percentage of correct reactions. •, Nomifensine; ○, alcohol; △, nomifensine plus alcohol. $***P < 0.001$; $*P < 0.05$.

administered double-blind. On each trial day the time schedule as shown in Figure 1 was used.

The quantitative data obtained were analyzed using the analysis of variance according to Friedmann and for each assessment period using Wilcoxon's paired comparison between the three treatments (Siegel, 1956).

Results

Physiological variables

In both alcohol conditions, heart rate and blood pressure (standing) were elevated and Romberg performance was impaired. There were no differences between alcohol alone and alcohol plus nomifensine, but these treatments were significantly different from nomifensine alone (Figure 2).

Behavioural variables

Multiple choice reaction time (determination apparatus) In the three variables measured (correct responses, correct but delayed responses, and mistakes) the detrimental effects of alcohol were remarkable, even 2 h after drinking.

No significant differences were found between both alcohol conditions, which were on the other side significantly different from nomifensine alone (Figures 3 and 4).

Simple reaction time (acoustic stimuli) Only under alcohol alone the prolongation of response latency was significantly different from nomifensine alone. There were no significant differences between both alcohol conditions (Figure 5).

Both-handed coordination With both variables, number of deviations and off-target time, the impairment of performance was significant in alcohol conditions, compared with nomifensine alone. No differences were found between both alcohol conditions (Figure 6).

Attention ('d-2' cancellation task) In both alcohol conditions the performance was significantly impaired, compared with nomifensine alone again with a lack of any difference between the alcohol conditions.

Interpretation With the exception of the perception threshold task which failed to produce any significant

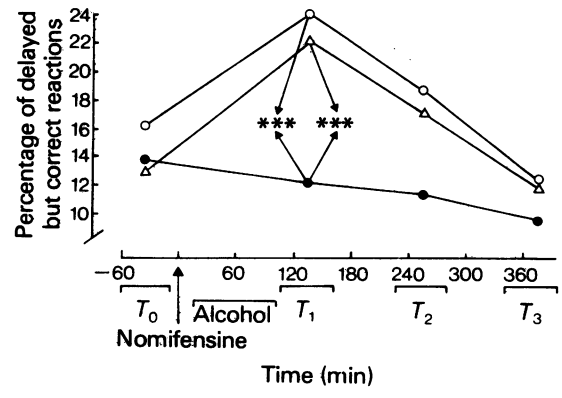

Figure 4 Multiple choice reaction task. Percentage of delayed but correct reactions. •, Nomifensine; ○, alcohol; △, nomifensine plus alcohol. $***P < 0.001$.

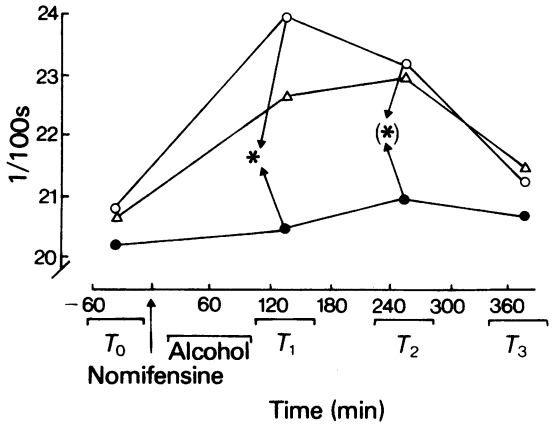

Figure 5 Latency of response to acoustic stimuli. •, Nomifensine; ○, alcohol; △, nomifensine plus alcohol. (*) $P < 0.01$; *$P < 0.05$.

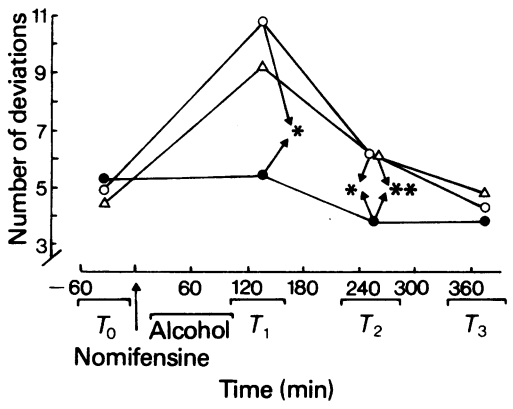

Figure 6 Both-handed coordination (tracking), number of deviations. •, Nomifensine; ○, alcohol; △, nomifensine plus alcohol. **$P < 0.01$; * $P < 0.05$.

results, all behavioural measurements have yielded unequivocal findings: the impairment of performance under alcohol was always significantly different from the effects of nomifensine. Between the effects of both alcohol conditions–that is, alcohol alone or together with nomifensine–there were no statistically significant differences at all. Numerically, the depressant effects were always more pronounced under alcohol alone so that a potentiation of alcohol effects by nomifensine can be excluded.

Subjective variables

The effects obtained with the 100-mm visual analogue scales used in this trial were hardly statistically different from random findings. This may be due to

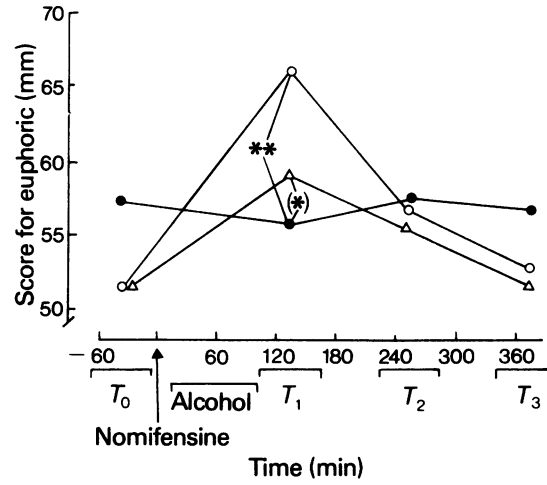

Figure 7 100-mm analogue scale depressed/euphoric. •, Nomifensine; ○, alcohol; △, nomifensine plus alcohol. **$P < 0.01$; (*) $P < 0.1$.

the insufficient reliability of such *ad hoc* instruments. The only significant effects were observed on the 'activity' and 'euphoria' scales, indicating that the subjects felt more active and euphoric when under the influence of alcohol (Figure 7). Side-effects like dizziness and headache were most frequently reported under alcohol plus nomifensine, and least frequently under nomifensine alone.

Conclusions

It was the objective of this trial to check whether nomifensine and alcohol, when taken together, have effects which are different from the effects of both agents taken alone. Our unequivocal findings permit the following conclusions.

(a) The effects of a combined administration of nomifensine and alcohol (impaired performance, increased pulse and blood pressure, increased feeling of activity, and euphoria) differed from the effects of nomifensine alone, as the monosubstance did not produce such changes.

(b) In the effects mentioned under (a) there were no differences between alcohol plus nomifensine, and alcohol alone. In no case was the impairment of functions stronger under the combination than it was under alcohol alone.

(c) As far as the experimental procedure described here allows for generalizations, it may be concluded that single administrations of nomifensine do not interact with the effects of alcohol especially not in the sense of an alcohol potentiation.

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