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Interaction of glutethimide and phenobarbitone with ethanol in man

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Interactions of ethanol with glutethimide and phenobarbitone in man were examined by means of psychomotor tests and measurement of ethanol and glutethimide in body fluids. Blood ethanol was about 11% higher overall when glutethimide and ethanol were given than in controls given ethanol alone, and 30% higher at 105 and 135 min. When phenobarbitone and ethanol were given there was a slight but significant reduction in blood ethanol. In the presence of ethanol there was a fall in plasma and urinary glutethimide. Changes in blood ethanol were reflected by changes in reaction time tests. Changes in plasma glutethimide were reflected by changes in tracking efficiency and finger tapping speed. These studies illustrate the need to assess drug concentrations in other interaction studies with ethanol and depressant drugs.

Many interactions between ethanol and other drugs in man have been documented but, on the evidence of Forney & Hughes (1968) few reports have included any reference to drug concentrations in body fluids, in spite of the fact that many drug interactions can be explained in terms of modifications of such concentrations. We have investigated aspects of the interaction of ethanol with two depressant drugs, glutethimide and phenobarbitone. Three experiments were made: (1) measurements of glutethimide in urine, ethanol in capillary blood, and performance in three psychomotor tests; (2) measurements of glutethimide and ethanol in venous plasma, after glutethimide and ethanol administration, and (3) measurements of ethanol in capillary blood after phenobarbitone and ethanol administration.

METHODS

Experiment 1: measurement of glutethimide in urine and of ethanol in whole blood

Four preparations were used: (A) 100 ml vodka (40% ethanol w/v) diluted with an equal volume of water flavoured with lime juice; (B) capsules containing only 250 mg glutethimide; (C) a "placebo" vodka drink, consisting of 10 ml vodka floated on the surface of 190 ml water flavoured with lime juice (this drink had a taste and smell similar to that of preparation (A); and (D) placebo capsules, containing lactose. In each session, four male and two female healthy subjects fasted for a minimum of 4 h before receiving one of four treatments: A + B; A + D; C + B; and C + D. The sessions were at least four days apart. Each subject attended four sessions, and the treatments were allocated on a double-blind, Latin square basis. The tests were conducted by a trained observer who did not known the nature of the treatments and who did not inform the subjects of the results of the tests*.

* Program of tests: −15 min psychomotor tests, 0 min consume capsule, +5 to + 15 min consume drink, + 15 min blood sample (thumb prick; 0·1 ml), psychomotor tests, +45 min blood sample, +75 min blood sample, psychomotor tests, +105 min blood sample; urine sample, psychomotor tests (not finger tapping), +135 min blood sample, psychomotor tests, +165 min blood sample, urine sample. The sequence of psychomotor tests consisted of: (1) tracking efficiency (3 min); (2) reaction time (2 min); (3) finger tapping (1 min); (4) reaction time (2 min); (5) tracking efficiency (3 min).

Experiment 2: measurement of glutethimide in plasma and of ethanol in whole blood

Two preparations were used: (A) 50 ml whisky (39% w/v ethanol) diluted with an equal quantity of water; and (B) tablets containing 250 mg glutethimide. In each session, two male healthy subjects and one female healthy subject fasted for a minimum of 4 h before receiving either the glutethimide alone or the combination. The two sessions for each subject were one week apart. The whisky was drunk as quickly as possible, and where both drugs were taken they were taken together. Venous blood samples were collected at 0·5, 1·0, 1·5 and 2·5 h after dosing.

Experiment 3: measurement of ethanol in whole blood after phenobarbitone

Two preparations were used: (A) 50 ml vodka diluted with an equal volume of water flavoured with lime juice; and (B) capsules containing 30 mg phenobarbitone, as the sodium salt. In each session, four male and two female healthy subjects fasted for a minimum of 4 h before receiving either the ethanol alone or the ethanol plus 60 mg phenobarbitone. The two sessions for each subject were one week apart. The vodka was drunk over 5 min; phenobarbitone was administered 30 min before the ethanol dose. Capillary blood samples were collected at 5, 15, 30, 60 and 90 min after the commencement of the ethanol dose.

Chemical determinations

Plasma and urinary glutethimide were measured in 5 ml aliquots by extraction of unmetabolized drug, concentration of the extracts, and gas-chromatography of the concentrates (Grieveson & Gordon, 1969). Blood ethanol was measured in 0·1 ml samples after adding them to 0·5 ml of aqueous n-propanol. Ethanol was estimated by gas-chromatography of the dilutions, using n-propanol as an internal standard (Curry, A. S., Walker & Simpson, 1967). It was shown in preliminary experiments that the presence of glutethimide and phenobarbitone in whole blood did not affect ethanol assays, and that ethanol did not interfere with the glutethimide analyses.

Behavioural tests

(*a*) Simple auditory reaction time. The time for the subject to depress a morse key on hearing a predetermined signal was recorded electronically. The signal was repeated 20 times, twice in each sequence, and the mean time (in ms) was calculated. The difference of this time from the pretreatment time was then calculated. The interval between signals varied from 1–6 s and was randomized.

(*b*) Tracking efficiency. The subject followed a narrow moving line on a revolving drum (6 rev/min) with a pen-shaped instrument equipped with an electrical circuit The greater the accuracy of the tracking the higher the score. This test was performed twice in each sequence, and the mean score was calculated. The difference of this score from the pretreatment score was then calculated.

(*c*) Finger tapping. The subject depressed a morse key as rapidly as possible for 1 min after hearing a predetermined signal. The number of times the key was depressed was counted electronically, and the difference of this score from the pretreatment score was calculated.

Statistical methods

The results of the psychomotor tests and differences in concentrations were subjected to two-way analysis of variance based on a randomized block design to test for differences in the results following the various treatments and to allow for inter-subject variation. The two-tailed paired student *t*-test was then used to test for levels of significance of differences in concentrations of drugs, and in behavioural test scores, at similar time points.

RESULTS

The effect of glutethimide on blood ethanol concentrations

In experiment 1, two contrasting phenomena were observed. At 15, 45 and 75 min (see Fig. 1) the ethanol concentrations were not significantly different from

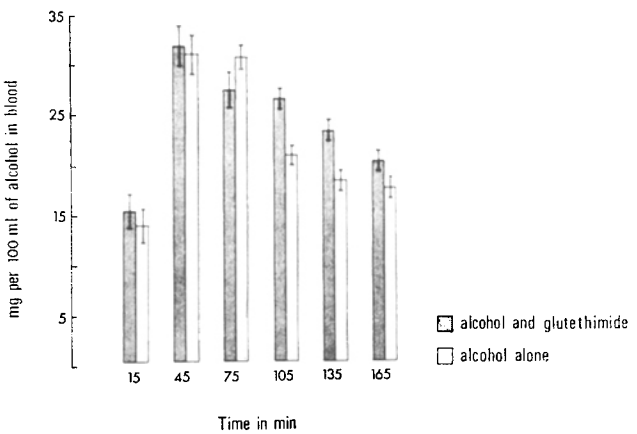

FIG. 1. Blood alcohol concentrations in six subjects treated with 100 ml vodka plus 250 mg of glutethimide, and with the vodka alone (Mean ± s.e.)

each other ($P > 0{\cdot}5$ at each time). At 105, 135 and 165 min there was a significantly higher ethanol concentration after the combination treatment ($P < 0{\cdot}01$ at each time point). The difference in the overall mean concentrations was 11%. Moreover, out of the 36 possible comparisons of blood ethanol concentrations, only 12 showed a lower concentration after the combination treatment.

To evaluate placebo treatments, a similar experiment was made during which the subject and the experimenter recorded their opinion at the end of each session concerning the treatment each subject had received. The experimenter was correct in his assessment 9/24 times and the subjects 15/24 times. The higher dose of ethanol was always detected but this was not so for the combination treatment.

In Experiment 2 the overall mean blood ethanol concentration following 50 ml of whisky alone was very low at 1·2 mg/100 ml; this should be compared with the analogous concentration of 21·3 mg/100 ml in Experiment 1 after 100 ml of vodka alone. In Experiment 2 the overall mean concentration after combination treatment was increased to 11·4 mg/100 ml.

The effect of ethanol on glutethimide concentrations in urine and plasma

The influence of ethanol on urinary glutethimide is shown in the following results. Urinary glutethimide (μg/ml) after 1·75 h was 0·24 ± 0·03 for the drug alone and 0·11 ± 0·01 after the drug and ethanol; respective figures for 2·75 h were 0·29 ± 0·03 and 0·07 ± 0·01 (n = 3). Thus there was a lower concentration of glutethimide in the urine after the combination treatment than after the drug alone. Each figure is mean ± s.e.; this difference was significant at both times ($P < 0·001$). As there is a direct linear relation between plasma concentration and urinary concentration (Curry, S. H., Riddall & others, 1971), lower plasma glutethimide concentrations during combination treatment can be expected. This we found to occur from the data collected from three subjects in whom we found the glutethimide concentrations (mean ± s.e.) to be as follows:

Time	0·5 h	1 h	1·5 h	2·5 h
Glutethimide and ethanol	0·65 ± 0·04	1·30 ± 0·06	0·90 ± 0·05	0·84 ± 0·01
Glutethimide	0·96 ± 0·03	1·45 ± 0·08	1·89 ± 0·07	1·24 ± 0·05

Thus the glutethimide concentrations were lower at each time point after the combination treatment although the differences at 0·5 h and 1 h were not significant, whereas at 1·5 and 2·5 h they were significant ($P < 0·05$).

Psychomotor tests

(*a*) Reaction time. The mean changes in reaction time from the pretreatment time for the four treatments in Experiment 1 are shown in Fig. 2. Treatments were

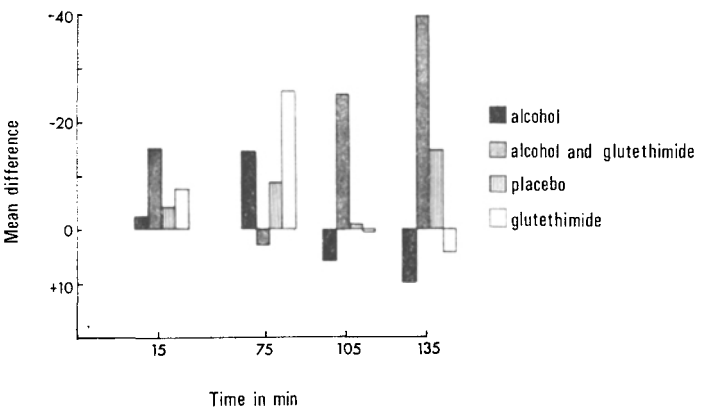

FIG. 2. Mean differences in reaction time in six subjects treated with 100 ml vodka, 100 ml vodka plus 250 mg of glutethimide, placebos, and the glutethimide alone. Mean pretreatment time = 292 ± 8 ms.

shown by analysis of variance to differ ($P < 0·005$), but this was due to the combination treatment producing the largest overall slowing of reaction time; the time was significantly different from that following the other treatments at 105 and 135 min ($P < 0·01$).

(*b*) Tracking procedure. The effects of the various treatments on tracking procedure are shown in Fig. 3. A significant deterioration in ability was caused only by the glutethimide alone. The treatments were shown by analysis of variance to be

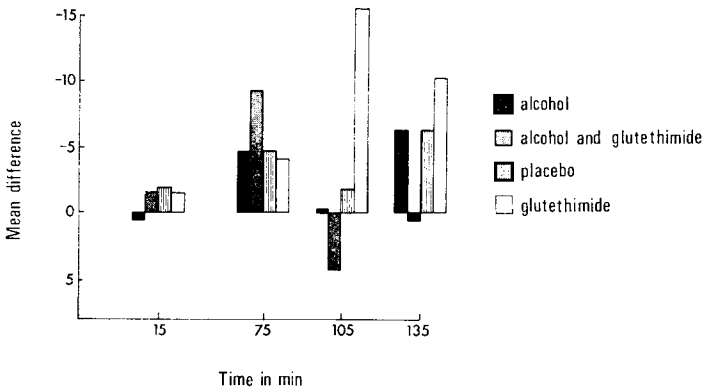

FIG. 3. Mean differences in tracking efficiency in the six subjects of Fig. 2. Mean pretreatment score = 168 ± 3.

not significantly different from each other ($P > 0{\cdot}05$ but $<0{\cdot}1$) but the deterioration in tracking after glutethimide at 105 and 135 min was significantly different from that after placebo treatment ($P < 0{\cdot}01$).

(*c*) Finger tapping. The results obtained from the four treatments are shown in Fig. 4. The treatments were shown by analysis of variance to differ in number of taps recorded ($P < 0{\cdot}05$). The difference was due to the glutethimide alone treatment, which showed a significantly lower number of taps at 75 and 135 min compared with the other treatments ($P < 0{\cdot}005$).

Effect of phenobarbitone on blood concentrations of ethanol

In contrast to the results above, 60 mg phenobarbitone produced an overall decrease in blood ethanol concentrations (figures are mean mg/100 ml ± s.e.):

Time	5 min	15 min	30 min	60 min	90 min
Ethanol + phenobarbitone ..	3·0 ± 1·2	10·2 ± 2·6	14·8 ± 2·2	11·2 ± 1·8	5·6 ± 1·4
Ethanol	3·7 ± 1·0	10·7 ± 0·8	17·7 ± 1·1	11·5 ± 1·0	8·2 ± 1·3

Although this decrease was not significant, the difference in the blood concentrations due to combination and ethanol alone treatment was significant at 30 and 90 min ($P < 0{\cdot}01$). Furthermore, out of 30 possible comparisons, 18 produced a decrease in blood ethanol after the combination.

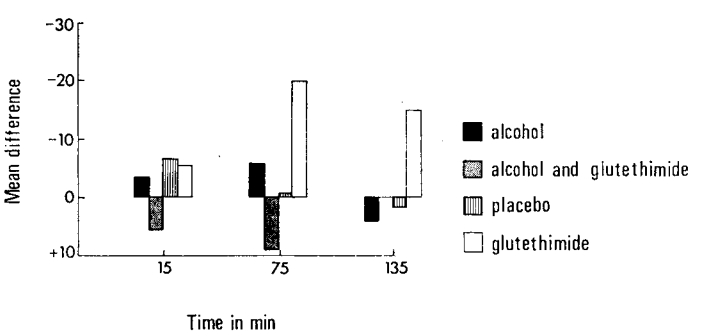

FIG. 4. Mean differences in finger tapping scores in the six subjects of Fig. 2. Mean pretreatment score = 353 ± 9.

DISCUSSION

The nature of these experiments was dictated by the assessments possible. Thus, Experiment 1 did not involve measurement of glutethimide in plasma, as venous samples are needed for this assay and the collection of such samples would have caused a variable trauma of sufficient intensity to affect the results of psychomotor tests. Instead, urinary glutethimide was assessed, as it has been shown separately that urinary and plasma glutethimide vary proportionately (Curry, S. H. & others, 1971). The influence of ethanol on plasma glutethimide was assessed separately (Experiment 2). Experiment 3 involved only ethanol assays, as no chemical method capable of measuring plasma phenobarbitone following small single doses is available at present. For safety reasons, in all experiments, the smallest ethanol and depressant drug doses compatible with a useful experiment were used.

To summarize, there was an increase in blood ethanol when glutethimide was given with ethanol. Overall, in Experiment 1, this increase was only 11% but it was nearer 30% at the three later times, while there was a marked decrease in plasma and urinary glutethimide following the combination. Phenobarbitone caused a small but significant decrease in blood ethanol. The reaction time test was apparently insensitive to the doses of ethanol or glutethimide used alone but was affected when the drugs were given in combination. The impairment was probably caused by the ethanol since blood ethanol was higher than that after ethanol alone, whereas the plasma concentration of glutethimide was lower than that after glutethimide alone.

The tracking and finger tapping tests showed analogous results. Both tests showed greatest impairment after glutethimide alone, and this impairment was reversed by ethanol, which also reduced plasma glutethimide. Thus ethanol inhibited these effects of glutethimide, by reducing the plasma concentration of the drug.

These data contribute to the understanding of interactions between ethanol and depressant drugs in several ways. They: (*a*) demonstrate the occurrence of several interactions; (*b*) illustrate the possibility of the interactions resulting from changes in drug concentrations; and (*c*) point to a possible difference in behavioural tests, shown by reaction time apparently being most sensitive to ethanol, and tracking and finger tapping apparently being most sensitive to glutethimide.

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