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TRAFFIC ACCIDENT RESEARCH UNIT

ALCOHOL, DRUGS AND ACCIDENT RISK

SECOND REPORT

DEPARTMENT OF MOTOR TRANSPORT NEW SOUTH WALES

The Traffic Accident Research Unit was established within the Department of Motor Transport, New South Wales, in May 1969 to provide a scientific approach to the traffic accident problem.

This paper is one of a number which report the results of research work undertaken by the Unit's team of medical, statistical, engineering and other scientists and is published for the information of all those interested in the prevention of traffic accidents and the amelioration of their effects.

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Commissioner.

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SECOND REPORT

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Abstract

The psychomotor effects of seven commonly used drugs, both licit and illicit, have been examined in human volunteers when given alone and in combination with alcohol. The drugs include Δ^9-Tetrahydrocannabinol (the main psychoactive principle of marihuana), two minor analgesics (aspirin and paracetamol), a preparation for the treatment of the common cold (Contac 500), a drug (allopurinol) taken for the treatment of gout, and disodium cromoglycate which is used to relieve the symptoms of asthma and allergic rhinitis.

A total of 139 subjects participated in these trials, many attending the laboratory on four occasions, and fourteen perceptual, cognitive and motor function tests, designed to correlate with driving skills, were carried out both before and after the consumption of drugs and/or alcohol. Briefly, the results showed that:

1) Tetrahydrocannabinol reduced performance across the test battery and, even at a subthreshold dose, increased alcohol-induced impairment.

2) Aspirin and paracetamol had no adverse influence on performance when given alone and did not modify the effects of alcohol.

3) Contac 500 was also without effect on performance in the tests and did not enhance alcohol-induced impairment.*

4) A tentative conclusion was reached that allopurinol may reduce the body's ability to metabolise alcohol.

5) Disodium cromoglycate did not enhance impairment due to alcohol and had no effects on performance when given alone.

* Note: 2) and 3) indicate that drivers may treat their symptoms without any obvious risk of affecting their ability to handle a motor vehicle.

1. INTRODUCTION

Driving a motor vehicle is a complex perceptual-motor task which involves the reception and integration of diverse sensory inputs, decision-making and the execution of manoeuvres of varying complexity. Such a sequence of events is clearly open to modification by drugs and social euphoriants such as alcohol and marihuana.

The consumption of alcohol and marihuana is widespread and increasing within the community as is the use of drugs both prescribed and obtained over the counter, e.g. antihistamines and minor analgesics. The role of alcohol in precipitating traffic crashes and fatalities is incontrovertible.

The main effect of alcohol appears to be its ability to depress the functions of the central nervous system. This effect is rather like that of the general anaesthetics to which pharmacological category alcohol belongs. Associated factors are disinhibition, the release of aggression and increased risk-taking. In addition, alcohol may further impair driver performance by disturbing the function of other physiological systems. For example, in a fasting subject, alcohol may lower the blood sugar concentration causing dizziness. Although these secondary effects are usually of minor importance when alcohol is consumed alone, it is thought that they may assume greater significance when drugs are also taken.

The role of drugs, however, taken alone or together with alcohol, is much more difficult to pinpoint. A number of facts deserve mention:

a) Drugs are mainly prescribed to treat symptoms and, in most cases, a driver may be presumed to be safer with his medication than without it. Nevertheless, the fact remains that the drug effect is superimposed on a disease state which may also be of relevance.

b) Patient compliance is not good - it is usually estimated at about 50% - and bizarre effects may arise from overdosage in an attempt to hasten recovery.

c) Patients reserve the right to treat apparently unrelated symptoms with over-the-counter drugs.

d) All drug treatments are superimposed on a 'normal' drug intake of caffeine, nicotine, alcohol and (increasingly), cannabis.

e) There are no limits for drug concentrations allowable in drivers and, in most cases, there is no procedure for measuring them.

The number of drugs which an individual may have prescribed or choose to purchase is very large indeed. In Australia, there are some 2000-3000 prescription items without counting generics and hospital packs. There are about the same number of over-the-counter preparations (which are admittedly drawn from a more limited range of ingredients) and an unknown contribution from fringe medicine.

It has been stated by Havard[1] that in technically developed countries, every doctor should assume that a patient will drive a motor vehicle unless proved otherwise. Thus, in order to provide meaningful advice to his patient, the doctor must also be aware of the likely effects of the drugs he prescribes on driving performance, both alone and when combined with alcohol. In most cases, this information is just not available to him.

A joint research programme has been initiated by the Traffic Accident Research Unit of the New South Wales Department of Motor Transport and the Department of Pharmacology at the University of Sydney to investigate alcohol-drug interaction.

The objective of this programme is to provide information on the effects of alcohol and other drugs, taken alone and in combination, on human cognitive, perceptual and motor performance measures which relate to driving skills.

The information gained from this programme will be of great benefit to the general public who remain largely unaware that prescribed or self-administered drugs may affect their driving performance. They are also unaware that drugs which do not reduce perceptual-motor performance by themselves may do so when combined with alcohol.

The information will also be of considerable use to the doctor in the management of individual patients and to the Department of Motor Transport in the prediction of traffic crash risk.

Seven relevant facts emerged from the first set of experiments in this programme.[2] These are as follows:

1. Impairment of human performance by alcohol was found to be dose-dependent for most of the perceptual, motor and cognitive tasks used.

2. The rate of alcohol metabolism was not increased and the alcohol-induced performance decrements were not reduced by large oral doses of fructose.

3. Caffeine in coffee, taken after alcohol, had no general 'sobering up' effect. Only the reaction time decrement was partially reversed by caffeine and performance in all other tasks remained impaired.

4. The antihistamine, dexchlorpheniramine (Polaramine) slightly reduced performance when given alone and both increased the alcohol-induced performance decrement and delayed recovery.

5. Another antihistamine, clemastine (Tavegyl), in sharp contrast, neither had effects when given alone or modified alcohol-induced impairment.

6. Diazepam (Valium) and alcohol had a supra-additive interaction.

7. Chlordiazepoxide (Librium), another minor tranquilliser, used for much the same purposes as diazepam, had less pronounced effects.

The conclusions were thus:

(a) That fructose was of no real value to a drink-driver in his attempt to sober up.

(b) That coffee before the 'drive home' was liable to induce a false sense of security.

(c) That some but not all antihistamines have sedative effects and that blanket warning labelling may be less appropriate than was formerly assumed.

(d) That important differences exist between the interactive effects of the two most commonly used tranquillisers with alcohol.

The present report presents the findings of studies on the interactive effects of alcohol with:

(a) Δ^9-tetrahydrocannabinol (THC), the psychoactive principle of marihuana.

(b) The two most commonly used non-narcotic analgesics, aspirin and paracetamol.

(c) Contac 500, a preparation taken for the relief of the symptoms of the common cold. The ingredients of this preparation are: phenylpropanolamine 50mg; alkaloids of belladonna 0.25mg.

(d) Allopurinol (Zyloprim), a drug which is prescribed to prevent attacks of gout.

(e) Disodium cromoglycate (Intal), which is prescribed largely for the treatment of asthma.

1.1. General Methodology

The methods used in the investigations presented in this report are similar to those detailed in the first report. A brief description of the tests is given in Appendix 2. The experimental designs were of two types (Figure 1.1): (1) dependent control experiment, in which each subject received four drug treatments at four different times administered in a Latin square order and (2) an independent control experiment, in which each subject was randomly assigned to one of four treatment groups and received only one treatment. The description of the test battery, the tests of reliability, the method of blood collection and the analysis of blood alcohol concentration used in the investigations have been described in detail by Franks et al.[3] An analysis of covariance[4] was performed on the results and where significant F-Values were obtained, a "Students" t-test was used to determine which treatment differences were significant. The significance level was set at $P < 0.05$.

Day No.	Group	Treatment	
Dependent Control			
1	A	Alcohol + Drug	Independent Control
	B	Alcohol + Drug Placebo *	
	C	Alcohol Placebo + Drug	
	D	Alcohol Placebo + Drug Placebo	
2	A	Alcohol + Drug Placebo	
	B	Alcohol + Drug	
	C	Alcohol + Drug Placebo	
	D	Alcohol Placebo + Drug	
3	A	Alcohol Placebo + Drug	
	B	Alcohol Placebo + Drug Placebo	
	C	Alcohol + Drug	
	D	Alcohol + Drug Placebo	
4	A	Alcohol Placebo + Drug Placebo	
	B	Alcohol Placebo + Drug	
	C	Alcohol + Drug Placebo	
	D	Alcohol + Drug	

Figure 1.1: The types of experimental design used in the studies.

* A drug placebo is an identical dose-form which contains no active drug.

The rest of this report contains a detailed technical account of each experiment and a discussion of the results. The conclusions that may be drawn from experimental findings may be found on pages 26-27.

2. THE INTERACTION OF ALCOHOL AND Δ^9-TETRAHYDROCANNABINOL (THC) (WHICH IS THE MAIN PSYCHOACTIVE PRINCIPLE OF MARIHUANA)

2.1 Introduction

Marihuana (Cannabis) consists of the dried leaves and flowering tops of the plant *Cannabis sativa*,[5] which is commonly known as Indian hemp. The medicinal use of Cannabis preparations can be traced back more than 5,000 years.[6] It was introduced into Western medicine by a Dr. W.B. O'Shaughnessy in]840 as a painkiller and a muscular relaxant. It was also used to treat epilepsy in children.[7] It is interesting to note that these properties are very similar to those of the minor tranquillisers, Librium and Valium, the widespread use of which was commented upon in the previous report.

Since marihuana and its derivatives have been shown to impair human sensory,[8,12] intellectual[13-17] and motor[13,18-20] functions, its possible involvement in increasing traffic accident risk is self-evident. Although a number of comparative studies on the effects of marihuana and alcohol have been carried out,[12,17,18,20-22] little attention has been directed towards the combined effects of the two drugs. This we consider to be most important since it has been reported that marihuana is often used concurrently with alcohol.[23]

This section of the report presents the findings obtained in two experiments which monitored the psychomotor effects of two "social" doses of THC after administration alone and when combined with a "social" dose of alcohol.

2.2. Method

2.2.1 Subjects

In both experiments, healthy, paid university student volunteers of both sexes were used. They had a mild to moderate marihuana smoking pattern ranging from 1-2 cigarettes per week to 2-3 cigarettes per day and had a mild drinking history (average = 570 ml of beer per day or its equivalent in wine or spirits). Before the first day of the experiment, all subjects were examined by a medical officer to ensure that no past or present illness or disability precluded their participation and the purpose of the experiment and its design were fully explained to them. The details of the subjects are given in Table 2.1.

Table 2.1: Details of subjects used in the 2 experiments on the interactive effects of alcohol and THC.

	Experiment I	Experiment II
Sex	8 males, 4 females	10 males, 4 females
Age	18 - 29 years (mean = 21.4 years)	18 - 32 years (mean = 23.7 years)
Body weight	59 - 74 kg (mean = 61.2 kg)	53 - 77 kg (mean = 61.9 kg)

2.2.2. Method of drug administration and dose levels

Since it has been shown that the amount of tetrahydrocannabinol (THC) which is absorbed from smoked marihuana can vary from 15 to 50% of its content,[24] it was decided to administer the drug orally. THC dissolved in sesame oil has been shown to be reliably absorbed after

oral administration, peak serum concentrations occurring after 1-3 hours.[25] Hence, THC was dissolved in sesame oil and sealed into capsules. Placebo capsules contained only sesame oil. The doses used were 0.14 mg/kg body weight in Experiment I, and 0.21 mg/kg body weight in Experiment II. These doses of THC were based on data reported by others.[25-26] The alcohol dose was 0.54 g/kg body weight in both cases and was given as a beverage containing 20% v/v ethanol in lemon squash. Alcohol was omitted from the placebo beverage.

2.2.3 Procedure

In both experiments, a dependent control design was used. Each subject received each of the four drug treatments; (1) alcohol plus THC placebo; (2) THC plus alcohol placebo; (3) alcohol plus THC; (4) alcohol placebo plus THC placebo. Both experiments were conducted on four consecutive Sundays following a Latin square order and were double-blind in that neither the subjects nor the observers were aware of which treatment had been administered until the series was complete. In addition, self-estimates of mood changes induced by the drug treatments were determined by the use of the P.O.M.S. (Profile of Mood States) mood rating scale (Educational and Industrial Testing Service, San Diego, U.S.A.). This checklist gives a mood rating for tension/anxiety; depression/dejection; anger/hostility; vigour and fatigue.

The subjects arrived at the laboratory approximately two hours after consuming a light breakfast. The test battery was administered to each subject before any drug treatment was given. After the control run, the subjects received two capsules to provide the required dose of

THC or placebo. One hour later, the subjects were given their beverage and consumed it under supervision over a 20 min period at a constant rate. Twenty minutes after drinking had finished, the subjects went through the test battery again but this time, blood samples were withdrawn at the mid-point of the sequence. This procedure was repeated twice at hourly intervals. The subjects were allowed to mingle freely but the tests were conducted in separate cubicles to reduce subject-subject interaction. Immediately after completing both the control and first post-alcohol (40 minute) test runs, each subject was required to fill in a P.O.M.S. questionnaire. A light lunch of sandwiches and de-caffeineated coffee was consumed after the second post-alcohol run.

2.3 Results

Experiment I

The results are presented in detail in Tables 2.2 - 2.4 in Appendix 1. Subjects who received both alcohol and THC had higher blood alcohol concentrations than when they received the same dose of alcohol alone. The difference was significant at the first time-point (40 minutes, $P < 0.05$) and a trend was evident thereafter.

A dose of 0.54 g/kg of alcohol did not induce statistically significant impairment in any of the tests when given alone. Similarly, a low dose of THC given alone was almost without effect. Significant impairment was only encountered in the perceptual speed test (errors) at 40 minutes and in a parameter measured on the Vienna Determination Apparatus (errors).

A combination of THC (0.]4 mg/kg) and alcohol, however, caused a significant decrease in performance in most tests. The results of the P.O.M.S. mood rating scale (not shown) were considered interesting in that there are many anecdotal reports which suggest that THC is a more pleasant social drug than alcohol. If anything, the reverse was indicated in this experiment which may, however, only reflect the setting in which the drugs were consumed and highlight the difficulty of work in this area.

Experiment II

The results are detailed in Tables 2.5 - 2.7 in Appendix 1. Unlike the results of the first experiment, there were no significant differences in the blood alcohol concentrations attained by the subjects, whether they received THC or not.

Again, this dose of alcohol (0.54 g/kg) produced slight impairment but the higher dose of THC (0.21 mg/kg) induced performance decrements in a number of tests, especially towards the end of the experiment (160 minutes).

The drug combination initially caused a fall-off in performance which was much worse than that induced by either of the components when taken alone. However, a degree of antagonism was evident in several of the tests, standing steadiness (eyes closed) and Vienna Determination Apparatus (errors) at 160 minutes and AKTG numerical reasoning (correct responses) at 100 minutes. The findings of the two studies can be summarised as follows:

1) A social dose of alcohol (0.54 g/kg) which induced a peak blood alcohol concentration of 60 mg/100 ml had only a slight effect on human cognitive, perceptual and motor functions.

2) The depressant effects of THC were dose-dependent, i.e. the higher dose (0.21 mg/kg) had more pronounced effects than the lower dose (0.14 mg/kg).

3) The performance decrement resulting from the combined effects of THC and alcohol was readily measurable and was suggestive of synergism, i.e. the combined effect of the drug combination was greater than would have been expected from the sum of the effects of its components.

4) A degree of antagonism between the higher dose of THC (0.21 mg/kg) and alcohol (0.54 g/kg) was apparent late in the course of the second experiment.

2.4 Discussion

The results of Experiment I indicated that the low THC dose produced a slight impairment which was comparable to that induced by an alcohol dose which was equivalent to about four middies of beer* or four glasses of wine or four whiskies. It was also shown that the interactive effect of alcohol and THC was at least additive with the lower dose of THC.

Experiment II showed that after increasing the THC dose by 50 per cent, the detrimental effects of the drug were clearly apparent. It is interesting to note that, in most cases, significant effects were not observed until about two hours after THC administration.

The finding of a degree of antagonism between the higher dose of THC and alcohol late in the course of the experiment confirms the results of others who have found the interaction between THC and

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* A middy of beer is equivalent to 285 millitres with 3.659/100 ml alcohol content.

alcohol to be complex. For example, it was found that a low dose of THC enhanced alcohol-induced motor impairment in the rat but higher doses reversed this enhancement.[27]

The precise nature of the interaction between alcohol and THC thus remains to be established but probably depends both on the relative doses of the two drugs and their separation in time. It is considered that these findings open up an interesting new field of investigation which is of great potential importance, both socially and experimentally. The fact that the role of marihuana in the traffic accident situation has not been evaluated and that mixed intoxication occurs[23] would appear to indicate a need for high priority to be given to further studies.

3. THE INTERACTION OF ALCOHOL WITH MINOR ANALGESICS

3.1 Introduction

The non-narcotic analgesics, which are effective in relieving mild to moderate pain, are widely used and have been frequently subject to abuse in Australia. The Australian Department of Health reported that during 1973-74, nearly 8 million prescriptions for non-narcotic analgesics were dispensed.[28] This figure does not, however, represent more than a fraction of the total usage because the popular brands are either available from pharmacies without prescription and from a wide variety of other outlets (garages, milkbars, supermarkets). Some indication of the consumption of these drugs by the Australian population can be gained from the results of surveys.[29 33] For example, in Brisbane and Sydney 43% of adults took an analgesic at least once a month and, in Canberra, the figure was 40%.[31 33] At the

upper end of the usage scale, it would appear that about 11% of the surveyed population took analgesics daily or at least several times a week.

Epidemiological research on the influence of alcohol and analgesic combinations on road accident risk is minimal. A study in Santa Clara County, U.S.A.[34] revealed that of 10,436 drink-drivers who were arrested, about 25% (2,599) were reported to have been on drug medication. Of these, about 12% (315) had taken analgesics or antipyretics. The only information available in Australia on drink-drivers who were concurrently on analgesic medication indicated that about 20% of those who were Breathalysed in 1972-73 in New South Wales[2] had taken these drugs.

However, despite this fact, little attention has been given to the influence of such drug combinations on human performance. This section reports the effects on psychomotor performance of two analgesics, aspirin and paracetamol, taken alone and in combination with alcohol.

3.2 Method

The independent control experimental design was used for both the aspirin and paracetamol study. The subjects were healthy male and female medical students aged between 20-27 years. 26 subjects per group were used in the aspirin experiment and 20 in the paracetamol experiment. Aspirin (990 mg) and paracetamol (100^{o} mg) or the appropriate placebos were given in capsules one hour prior to consuming either an alcoholic beverage or a placebo drink. In both experiments, a dose of 0.75 g/kg body weight of alcohol, which was presented as a 20% v/v

solution in orange squash, was used. Capillary blood samples were taken for measurement of blood alcohol concentrations.

3.3. Results

(1) Aspirin

The performance of subjects who received aspirin (990 mg) was not significantly different from those who received placebo (Table 3.1 F). This dose of alcohol (0.75 g/kg) produced a peak blood alcohol concentration of 0.09 g/100 ml. Aspirin had no significant modifying effect on the blood alcohol concentrations attained (Table 3.2).

Alcohol induced significant impairment in most of the tests (Table 3.1, columns D & E). However, the combination of aspirin with alcohol produced no significantly different effects from those of alcohol alone, except in complex reaction time where a degree of antagonism was apparent (Table 3.1, column A).

(2) Paracetamol

This dose of alcohol (0.75 g/kg) which again gave a peak blood alcohol concentration of 0.09 g/100 ml, caused significant impairment in performance in most of the tests (Table 3.3, columns D, E). Paracetamol(1000mg) had no significant effect on psychomotor performance (Table 3.3, column F) and did not modify alcohol-induced impairment except in the auditory reaction time and numerical reasoning (correct answers) tests (Table 3.3, column A) where a degree of synergism occurred. The blood alcohol concentrations attained by the subjects were not significantly modified by paracetamol pretreatment (Table 3.4).

3.4 Discussion

Neither aspirin nor paracetamol had significant effects on

psychomotor performance when given alone. When combined with a dose of alcohol which induced significant impairment across the test battery, performance in only two tests was modified by drug pretreatment. In the case of aspirin, complex reaction time was significantly decreased at two time points and with paracetamol, simple auditory reaction time was increased. The blood alcohol concentrations were unaffected by prior administration of either drug. The dose of aspirin used was in the middle of the therapeutic range and since patients under treatment for rheumatoid arthritis[35] receive much higher doses, it might be interesting to pursue this investigation further. Higher doses of paracetamol are, however, seldom administered. Neither drug would appear to pose a threat to driver safety either alone or mixed with alcohol in terms of psychomotor impairment.

4. THE INTERACTION OF ALCOHOL AND CONTAC 500

4.1 Introduction

Contac 500 is a compound sustained release preparation, which is widely available from pharmacies without prescription, for the treatment of the symptoms of the common cold. Its active constituents are: belladonna alkaloids (0.2 mg) and phenylpropanolamine hydrochloride (50 mg).

Because alcohol is also a popular home remedy for the treatment of colds, it is not unreasonable to suppose that drivers with colds may consume preparations, such as Contac 500, as well as alcohol in an attempt to cope with their infection. It was therefore considered of interest to determine whether Contac 500 had an effect on human psychomotor performance or whether it modified alcohol-induced impairment.

4.2 Method

An independent control experimental design was used with 29 healthy student volunteers in each treatment group. A Contac 500 capsule or an identical placebo capsule was taken 1 h before the administration of alcohol (0.75 g/kg body weight) which was presented as a 20% v/v solution in sugar-free orange squash. The alcohol placebo was orange squash. The drinks were consumed at a constant rate over a 20 min period. Capillary blood samples were taken for the estimation of blood alcohol concentrations.

4.3 Results

The results are given in Tables 4.1 and 4.2, from which it can be seen that Contac 500 alone significantly improved complex reaction time at 100 min but was without effect on the other performance measures. Alcohol, as expected, impaired performance in most of the tests (Table 4.1, column D) which was particularly apparent at the first testing time (40 min after beginning to drink alcohol).

Significant performance decrements were also seen after the administration of Contac 500 together with alcohol (Table 4.1, columns D and E). In two measures of performance, however (manual dexterity at 100 min; Vienna Determination Apparatus at 40 min), there was antagonism of the alcohol-induced decrement in performance (Table 4.1, column A). The blood alcohol concentrations attained by the subjects were not modified by pretreatment with Contac 500 (Table 4.2).

4.4 Discussion

The results obtained are consistent with the mild central nervous system stimulant effects of phenylpropanolamine at this dose level. Unlike preparations which contain certain antihistamines, which are also used for the treatment of coughs and colds, there is no evidence to suggest the need for warning labelling relating either to the effects of Contac 500 alone or when taken in combination with alcohol.

5. ALCOHOL AND ALLOPURINOL

5.1 Introduction

Allopurinol was first administered for the treatment of gout some ten years ago when its efficacy as a xanthine oxidase inhibitor became apparent.[36] Apart from its principal action on that enzyme, a number of secondary metabolic effects have subsequently been observed.

Furthermore, interaction of allopurinol with coumarin and with thiazide diuretics has been reported.[37-38] While the ultimate clinical significance of these effects remains uncertain, they clearly should be taken into consideration when other drugs are administered concurrently with allopurinol.

In view of such findings, we were prompted to consider the possibility of interaction between allopurinol and alcohol. A strong association between gout and alcohol consumption in the Australian population has been reported.[39-40] Thus in Australia at least, alcohol and allopurinol may frequently be ingested together, despite medical advice to the contrary. The opportunity was taken to set up a preliminary investigation in an attempt to assess the possibility of an allopurinol/alcohol interaction occurring in drivers.

5.2 Method

The subjects were paid university student volunteers (17 male, 4 female) from whom informed consent had been obtained. All had mild drinking histories and were not receiving any other drugs.

The subjects attended the laboratory on two occasions four weeks apart. On the first occasion, after the control tests had been administered and a blood sample taken for analysis, the subjects received alcohol (0.75 g/kg) in sugar-free orange squash which they consumed at a constant rate over a 20 minute period. Psychomotor tests were conducted 20 min after drinking finished and twice thereafter at hourly intervals. Capillary blood was taken at each time point for the measurement of blood alcohol concentrations and pyruvate:lactate ratios.

At the conclusion of the first day, the subjects were given bottles of either allopurinol or placebo tablets, in a random fashion. Instructions were to take one 100 mg tablet per day after the evening meal for the first three days, then three tablets a day in a single dose for the remainder of the 4 week period of the trial. Subjects were also asked to collect a 24 hour urine specimen on the last day of the trial. The same protocol was repeated at the end of 4 weeks with the addition that the subjects were asked to fill out a questionnaire relating to possible side effects arising from drug therapy and all were interviewed by a medical practitioner.

5.3 Results

Primary and secondary checks on drug consumption as well as careful questioning eliminated three subjects. The drug was well tolerated in the other subjects, the incidence of reported untoward effects being greater in the placebo- than in the drug-treated group. On the first day, a peak blood alcohol concentration of 89 mg/100 ml occurred at 40 minutes (Table 5.1). Blood alcohol concentrations tended to be higher on the second day, however. Significant differences only occurred for the allopurinol group receiving alcohol ($P < 0.01$ at 100 minutes and

$P < 0.05$ at 160 minutes). There were no significant differences between the performance of each group in the pre-drug trial. Subsequent analysis was therefore carried out using the control reading for each subject as the co-variate.

In most of the tests, there was a trend towards a greater impairment in the second trial only in the group which had received allopurinol for a month. In some cases the difference in performance in the two trials reached statistical significance as indicated in Table 5.2.

The tests may be separated into four groups dependent on the variation between the placebo and allopurinol group:

(A) Three of the tests in which there were no differences between the two groups. These were complex reaction time, numerical reasoning (errors) and perceptual speed (correct answers).

(B) Three tests in which trends were observed but which failed to show statistical significance. These were: standing steadiness (eyes open), manual dexterity and the Vienna determination apparatus (errors).

(C) Seven tests in which the allopurinol group performed worse than the placebo group and which showed statistical significance. These were standing steadiness (eyes closed), visual reaction time, auditory reaction time, numerical reasoning, perceptual speed (errors), Vienna determination apparatus (estimated correct) and verbal fluency.

(D) Two apparently anomalous results, Vienna determination apparatus (correct responses) and Vienna determination apparatus (delayed correct), in which the placebo group performed worse than the allopurinol group.

It should be noted that, with the exception of the standing steadiness test at 40 minutes in the allopurinol group, all tests that showed statistically significant differences did so at the later time periods.

5.4 Discussion

The results of this preliminary study lead to the conclusion that allopurinol therapy can give rise to small but significant changes in the metabolism of alcohol. The changes are manifested as differences in blood alcohol levels, and in decreased facility of the trial group in a number of the psychomotor tests. The latter effects may simply reflect the relatively increased blood alcohol levels of the test subjects though it is not possible at this stage to rule out other mechanisms.

It should be stressed that there are severe limitations associated with this study. Normally, such a trial would be carried out on a 4 x 4 Latin square basis with both drug and alcohol placebos. In particular, the present study has not allowed for the effects of allopurinol alone on the psychomotor tests.

However, such a systematic trial posed very considerable problems and would have taken approximately eight months to complete. Thus it was considered desirable to establish, in a relatively short period of time, guidelines to see if a systematic trial was justified. The results given above would appear to vindicate the decision.

It should also be noted that the subjects were young healthy adults and thus probably unrepresentative of the group normally ingesting both allopurinol and alcohol. It is hoped to carry out a complete trial with a more representative age group in the future.

6. INTERACTION OF ALCOHOL AND DISODIUM CROMOGLYCATE (DSCG)

6.1 Introduction

Disodium cromoglycate is used in the prophylactic treatment of asthma and rhinitis, particularly but not exclusively of the allergic type. It is thought to act by conferring stability to the mast cells and thus preventing the release of histamine and slow reacting substance-containing granules. Although there have been a number of human studies on the effects of the drug[41-45], none has investigated its effects on psychomotor performance, either alone or when combined with a social dose of alcohol. Since 8.3% of drivers who were Breathalyzed in NSW during the period 1972-73 stated that they were receiving treatment with drugs which have an effect on the respiratory system, it appeared to be appropriate to examine the interaction between disodium cromoglycate and alcohol.

6.2 Method

A 4 x 4 Latin square design was used in this experiment. The subjects were 17 healthy, paid university student volunteers of both sexes (6 female, 11 male) aged between 18 and 27 years. All had mild drinking histories and were not receiving any other drug medication. Disodium cromoglycate (DSCG) was presented as 20 mg capsules and was inhaled *via* a turbopropellor apparatus (Spinhaler) under the direction of a trained nursing sister. A dose of 40 mg was used. Placebo capsules contained lactose (35 mg) and sodium sulphate (5 mg). Alcohol (0.75 g/kg body weight) was given as a beverage containing 20% v/v alcohol in sugar-free orange squash. The placebo beverage was alcohol-free.

6.3 Results

The peak blood alcohol concentration reached 90 mg/100 ml (Table 6.1). Disodium cromoglycate did not significantly modify the blood concentration attained.

In general, subjects receiving DSCG showed no appreciable difference in performance as compared with the double placebo group (subjects receiving no alcohol or DSCG), except in auditory reaction time and perceptual speed (errors) where the DSCG subjects performed significantly better (Table 6.3).

Alcohol, either taken alone or with DSCG, induced significant impairment in most of the tests (Table 6.3). However, the effects of alcohol were not significantly altered by DSCG except on complex reaction time and perceptual speed (error) where an apparent antagonism was observed (Table 6.3).

The findings of this experiment indicated that the dose of alcohol (0.75 g/kg) induced significant decrements in performance as shown in previous experiments. The administration of disodium cromoglycate did not modify the blood alcohol concentrations attained nor, in general, the alcohol-induced decrements.

6.4 Discussion

The lack of significant effect on performance of disodium cromoglycate is not surprising since it has been shown not to cross the blood-brain barrier.[44] This indicates that the direct effects of DSCG are unlikely to affect the central nervous system. The results obtained in this experiment are for the interactive effects of a single dose of alcohol and DSCG.

It is possible that the interactive effects obtained after a period of continuous DSCG therapy may be different from those seen after a single dose. This is considered to be unlikely, however, because human excretion patterns of DSCG preclude cumulation.

However, a physician may now choose to treat a patient suffering from an appropriate complaint with disodium cromoglycate with the knowledge that, unlike certain antihistamines which may also be prescribed for the same purposes, the drug is unlikely to affect his driving ability.

7. CONCLUSIONS

Most drugs have no discernible effect on driver performance if taken alone and according to instructions. There is, however, a pressing need to identify those drugs which may reduce driving ability. There is also a need to identify potentially dangerous drug-alcohol interactions. There is no easy way to accomplish these aims apart from close investigation of drugs which are commonly used or those which appear as problems in the results of field studies. The results of this series of experiments can be summarised as follows:

1. The experiments with THC indicate that the drug is capable of reducing psychomotor performance when given alone and, even in subthreshold doses, interacts with alcohol in a manner which is at least additive. The use of marihuana in the population has been increasing[46-50] and it has been established that mixed intoxication with alcohol is common.[23] It is therefore considered highly desirable that further studies be mounted to determine the precise nature of marihuana intoxication and to attempt to define a correlate for blood marihuana concentrations which might be reasonably permitted in drivers (if the law were to be changed) which is similar to the prescribed limit for alcohol.

2. Two commonly used over-the-counter analgesics, aspirin and paracetamol, have been shown not to reduce psychomotor performance and not to interact in an adverse manner with alcohol. This has importance for drivers since these preparations are widely used to treat minor symptoms (e.g. headache) which may themselves increase accident risk.

3. A preparation for the treatment of the symptoms of the common cold, Contac 500, was shown to have no detrimental effects on performance in the test battery when given alone and not to increase alcohol-induced impairment. Again, the implications for the driver are that he can treat his symptoms with this preparation without a likelihood of impairment of his driving ability.

4. In a pilot study, it was shown that allopurinol, which is used to prevent attacks of gout, appears to pose problems in that it seems likely to be able to reduce the body's ability to handle alcohol. It must be stressed that this conclusion is only tentative and a more comprehensive study is required before an unequivocal conclusion can be drawn.

5. Hay fever and other forms of allergic rhinitis present a problem to many people at certain times of the year. Many drug treatments for these conditions induce sedation and/or potentiate the effects of alcohol. It has been clearly demonstrated that an effective treatment for allergic rhinitis, disodium cromoglycate, has negligible effects on psychomotor performance and does not modify alcohol-induced impairment.

TABLE 2.2: INTERACTION BETWEEN ALCOHOL (0.54G/KG) AND Δ^9-THC (0.14MG/KG)

BLOOD ALCOHOL CONCENTRATION

Treatment	Mean Blood Alcohol Concentration (mg/100 ml) ± S.E. (n = 12)		
	Time (min)		
	40	100	160
Alcohol + Δ^9-THC	73 ± 4	54 ± 3	34 ± 3
Alcohol + Placebo	63 ± 3	50 ± 3	29 ± 3

* P = 0.05

TABLE 2.3

F-RATIOS FOR DIFFERENCES BETWEEN CORRECTED TREATMENT MEANS OBTAINED BY ANALYSIS OF COVARIANCE

THC EXPERIMENT I

Test	F-ratio (df = 3, 29) After 40 min	After 100 min	After 160 min
Standing steadiness (eyes open)	5.080†	1.795	5.464†
Standing steadiness (eyes closed)	4.012*	1.730	6.499†
Simple visual reaction time	0.101	0.268	1.001
Simple auditory reaction time	0.679	0.185	2.393
Complex reaction time	0.131	1.198	0.805
Manual dexterity	2.551	0.106	1.458
Numerical reasoning:			
(a) correct answers	0.770	0.283	0.451
(b) errors	1.149	0.568	3.881*
Perceptual speed:			
(a) correct answers	1.503	0.908	1.034
(b) errors	3.552*	3.983*	0.709
Vienna Determination Apparatus:			
(a) correct responses	3.260*	2.007	0.355
(b) errors	4.937†	1.877	2.177
(c) estimated correct responses	3.858*	1.995	1.890
POMS mood rating scale:			
(a) tension/anxiety	1.646		
(b) fatigue	1.425		
(c) confusion/bewilderment	0.076		
(d) vigour	0.970		
(e) anger/hostility	2.046		
(f) depression/dejection	1.799		

* $P < 0.05$

† $P < 0.01$

TABLE 2.4

THE INTERACTION BETWEEN ETHANOL (0.54G/KG) AND Δ^9-TETRAHYDROCANNABINOL(0.14MG/KG): THE SIGNIFICANCE OF THE DIFFERENCES BETWEEN TREATMENT GROUPS (T-TESTS)

	COMPARISON																	
	A			B			C			D			E			F		
	(a) Alcohol + THC			(a) Alcohol + THC			(a) Alcohol + THC			(a) Alcohol			(a) Alcohol			(a) THC		
	v			v			v			v			v			v		
	(b) Alcohol			(b) THC			(b) Placebo			(b) THC			(b) Placebo			(b) Placebo		
Time (min) after alcohol drinking began	40	100	160	400	100	160	40	100	160	40	100	160	40	100	160	40	100	160
TEST																		
Standing steadiness (eyes open)	↓↓	-	↓↓	↓↓	-	↓↓	↓↓↓	↓↓	↓↓↓	-	-	-	-	-	-	-	-	-
Standing steadiness (eyes closed)	-	-	↓↓↓	↓↓	-	↓↓	↓↓↓	↓↓	↓↓↓	-	-	-	-	-	-	-	-	-
Manual dexterity	↓↓	-	-	↓↓	-	-	↓↓	-	-	-	-	-	-	-	-	-	-	-
Vienna Determination Apparatus																		
(a) correct responses	-	-	-	↓↓↓	↓↓	-	↓↓	-	-	-	-	-	-	-	-	-	-	-
(b) errors	↓↓	-	-	↓↓↓	-	-	↓↓↓	-	↓↓	-	-	-	-	-	-	-	-	↓↓
(c) estimated correct responses	-	-	↓↓	↓↓↓	↓↓	-	↓↓↓	↓↓	-	-	-	-	-	-	-	-	-	-
Complex reaction time	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Simple visual reaction time	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Simple auditory reaction time	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Numerical reasoning (correct answers)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Numerical reasoning (errors)	-	-	↓↓↓	-	-	-	-	-	↓↓	-	-	-	-	-	-	-	-	-
Perceptual speed (correct answers)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Perceptual speed (errors)	-	↓↓	-	-	↓↓↓	-	↓↓↓	↓↓	-	-	-	-	-	-	-	↓↓	-	-

↓↓ $P < 0.05$; ↓↓↓ $P < 0.01$

TABLE 2.5: INTERACTION BETWEEN ALCOHOL (0.54G/KG) AND Δ^9-THC (0.21MG/KG)

BLOOD ALCOHOL CONCENTRATION

Treatment	Mean Blood Alcohol Concentration (mg/100 ml) ± S.E. (n = 15)		
	Time (min)		
	40	100	160
Alcohol + Δ^9-THC	65 ± 4	49 ± 3	31 ± 2
Alcohol + Placebo	72 ± 4	53 ± 5	30 ± 3

TABLE 2.6

F-RATIOS FOR DIFFERENCES BETWEEN CORRECTED TREATMENT MEANS OBTAINED BY ANALYSIS OF COVARIANCE

THC EXPERIMENT II

Test	F-ratio (df = 3,36) After 40 min	After 100 min	After 160 min
Standing steadiness (eyes open)	7.878‡	1.173	1.272
Standing steadiness (eyes closed)	4.178	1.631	7.694‡
Complex reaction time	0.223	1.773	0.605
Simple visual reaction time	1.100	1.221	1.744
Simple auditory reaction time	0.492	2.442*	2.404*
Manual dexterity	2.737†	1.887	2.269*
Numerical reasoning (correct)	4.570‡	1.570	0.400
Numerical reasoning (errors)	3.630†	4.711‡	0.815
Perceptual speed (correct)	0.634	0.757	1.439
Perceptual speed (errors)	1.789	0.472	1.620
Vienna Determination Apparatus:			
(a) correct responses	1.752	0.753	1.139
(b) errors	1.579	0.862	2.733*
(c) estimated correct responses	0.519	0.512	0.804
AKTG (correct)	5.135‡	2.962†	4.014†
AKTG (errors)	3.315†	1.538	3.640†

* $P < 0.1$

† $P < 0.05$

‡ $P < 0.01$

TABLE 2.7

INTERACTION BETWEEN ALCOHOL (0.54G/KG) AND Δ^9-TETRAHYDROCANNABINOL (0.21MG/KG): THE SIGNIFICANCE OF THE DIFFERENCES BETWEEN TREATMENT GROUPS (T-TESTS)

	COMPARISON																	
	A			B			C			D			E			F		
	(a) Alcohol + THC			(a) Alcohol + THC			(a) Alcohol + THC			(a) Alcohol			(a) Alcohol			(a) THC		
	v			v			v			v			v			v		
	(b) Alcohol			(b) THC			(b) Placebo			(b) THC			(b) Placebo			(b) Placebo		
Time (min) after alcohol drinking began	40	100	160	40	100	160	40	100	160	40	100	160	40	100	160	40	100	160
TEST																		
Standing steadiness (eyes open)	↓↓	–	–	–	–	–	↓↓↓	–	–	–	–	–	↓↓↓	–	–	↓↓	–	–
Standing steadiness (eyes closed)	–	–	↑↑	↓↓	–	–	↓↓	–	↓↓	↑↑	–	↑↑↑	–	–	–	↓↓	–	↓↓↓
Manual dexterity	–	–	–	–	–	–	↓↓	–	↓↓	–	–	–	↓↓	–	–	–	–	–
Vienna Determination Apparatus																		
(a) correct responses	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
(b) errors	–	–	↑↑	–	–	–	↓↓	–	–	–	–	–	–	–	–	–	–	↓↓
(c) estimated correct responses	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Complex reaction time	–	↓↓	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Simple visual reaction time	–	–	–	–	–	↓↓	–	–	–	–	–	–	–	–	–	–	–	–
Simple auditory reaction time	–	–	–	–	–	–	–	↓↓	–	–	–	–	–	–	–	–	↓↓	↓↓
Numerical reasoning (correct responses)	–	–	–	–	–	–	↓↓	–	–	–	–	–	↓↓↓	–	–	–	↓↓	–
Numerical reasoning (errors)	–	–	–	↓↓	–	–	↓↓↓	↓↓↓	–	–	–	–	–	↓↓↓	–	–	–	–
AKTG (correct answers)	↓↓↓	–	–	–	–	–	↓↓↓	–	↓↓	↓↓	–	↑↑	↓↓	–	–	–	↓↓	↓↓↓
AKTG (errors)	↓↓	↑↑	–	–	–	–	↓↓↓	–	↓↓↓	–	–	–	–	–	–	–	↓↓	–
Perceptual speed (correct answers)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Perceptual speed (errors)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	↓↓	–	–

↓↓ $P < 0.05$; ↓↓↓ $P < 0.01$

TABLE 3.1

THE INTERACTION BETWEEN ALCOHOL (0.75 G/KG) AND ASPIRIN (990 MG): THE SIGNIFICANCE OF THE DIFFERENCES BETWEEN TREATMENT GROUPS (T-TESTS)

	COMPARISON																	
	A			B			C			D			E			F		
	(a) Alcohol + Aspirin v (b) Alcohol			(a) Alcohol + Aspirin v (b) Aspirin			(a) Alcohol + Aspirin v (b) Placebo			(a) Alcohol v (b) Aspirin			(a) Alcohol v (b) Placebo			(a) Aspirin v (b) Placebo		
Time (min) after alcohol drinking began	40	100	160	40	100	160	40	100	160	40	100	160	40	100	160	40	100	160
TEST																		
Standing steadiness (eyes open)	-	-	-	↓↓	↓↓↓	-	↓↓	↓↓	-	↓↓	-	-	↓↓↓	↓↓	-	-	-	-
Standing steadiness (eyes closed)	-	-	-	↓↓↓	-	-	↓↓	↓↓	-	↓↓↓	-	-	↓↓	↓↓	-	-	-	-
Vienna Determination Apparatus																		
(a) correct responses	-	-	-	↓↓↓	↓↓↓	-	↓↓↓	↓↓↓	-	↓↓↓	↓↓↓	-	↓↓↓	↓↓↓	-	-	-	-
(b) errors	-	-	-	-	↓↓↓	-	↓↓	↓↓↓	-	↓↓↓	↓↓↓	-	↓↓↓	↓↓↓	-	-	-	-
(c) estimated correct responses	-	-	-	↓↓	-	-	↓↓↓	↓↓	-	↓↓↓	↓↓↓	-	↓↓↓	-	-	-	-	-
(d) delayed correct responses	-	-	-	↓↓↓	↓↓↓	-	↓↓	-	-	↓↓↓	-	-	↓↓↓	-	-	-	-	-
Complex reaction time	↑↑	↑↑↑	-	↓↓	-	-	↓↓↓	-	-	↓↓↓	-	-	-	-	-	-	-	-
Simple visual reaction time	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Simple auditory reaction time	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Numerical reasoning (correct responses)	-	-	-	↓↓↓	-	-	↓↓	-	-	↓↓↓	-	-	↓↓	-	-	-	-	-
Numerical reasoning (errors)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Perceptual speed (correct answers)	-	-	-	↓↓↓	-	-	↓↓	-	-	-	-	-	-	-	-	-	-	-
Perceptual speed (errors)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

↓↓ $P < 0.05$; ↓↓↓ $P < 0.01$

TABLE 3.2: INTERACTION BETWEEN ALCOHOL (0.75G/KG) AND ASPIRIN (990MG)

BLOOD ALCOHOL CONCENTRATION

Treatment	Mean Blood Alcohol Concentration (mg/100 ml) ± S.E. (n = 26)		
	Time (min)		
	40	100	160
Alcohol + aspirin	91 ± 5	91 ± 5	78 ± 5
Alcohol + placebo	92 ± 4	83 ± 5	72 ± 3

TABLE 3.3

THE INTERACTION BETWEEN ALCOHOL (0.75G/KG) AND PARACETAMOL (1.0G): THE SIGNIFICANCE OF THE DIFFERENCES BETWEEN TREATMENT GROUPS (T-TESTS)

	COMPARISON																	
	A			B			C			D			E			F		
	(a) Alcohol + Paracetamol v (b) Alcohol			(b) Alcohol + Paracetamol v (b) Paracetamol			(a) Alcohol + Paracetamol v (b) Placebo			(a) Alcohol v (b) Paracetamol			(a) Alcohol v (b) Placebo			(a) Paracetamol v (b) Placebo		
Time (min) after alcohol drinking began	40	100	160	40	100	160	40	100	160	40	100	160	40	100	160	40	100	160
TEST																		
Standing steadiness (eyes open)	-	-	-	↓↓	-	-	↓↓↓	-	-	↓↓↓	↓↓↓	-	↓↓↓	↓↓↓	-	-	-	-
Standing steadiness (eyes closed)	-	-	-	↓↓↓	↓↓↓	-	↓↓↓	↓↓↓	-	↓↓↓	↓↓	-	↓↓↓	↓↓↓	-	-	-	-
Manual dexterity	-	-	-	↓↓	-	-	↓↓↓	↓↓	-	↓↓	-	-	↓↓↓	↓↓	-	-	-	-
Vienna Determination Apparatus																		
(a) correct responses	-	-	-	↓↓	-	-	↓↓	↓↓	-	↓↓↓	↓↓	-	↓↓↓	↓↓↓	-	-	-	-
(b) errors	-	-	-	↓↓	-	-	↓↓↓	-	-	↓↓	-	-	↓↓	-	-	-	-	-
(c) estimated correct responses	-	-	-	↓↓	-	-	↓↓	↓↓	-	↓↓↓	↓↓	-	↓↓↓	↓↓↓	-	-	-	-
(d) delayed correct responses	-	-	-	↓↓	-	-	↓↓↓	-	-	↓↓	-	-	↓↓	-	-	-	-	-
Complex reaction time	-	-	-	↓↓	-	-	↓↓	-	-	-	-	-	-	-	-	-	-	-
Simple visual reaction time	-	-	-	-	-	-	↓↓	-	-	↓↓↓	-	-	↓↓	-	-	-	-	-
Simple auditory reaction time	↓↓	-	↓↓	↓↓↓	-	-	↓↓↓	-	↓↓↓	-	-	-	-	-	-	-	-	-
Numerical reasoning (correct responses)	-	↓↓	-	-	-	-	↓↓↓	↓↓↓	-	-	-	-	↓↓↓	↓↓	-	-	-	-
Numerical reasoning (errors)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

↓↓ $P < 0.05$; ↓↓↓ $P < 0.01$

TABLE 3.4: INTERACTION BETWEEN ALCOHOL (0.75G/KG) AND PARACETAMOL (1000MG)

BLOOD ALCOHOL CONCENTRATION

Treatment	Mean Blood Alcohol Concentration (mg/100 ml) ± S.E. (n = 20)		
	Time (min)		
	40	100	160
Alcohol + paracetamol	85 ± 5	86 ± 4	72 ± 3
Alcohol + placebo	86 ± 8	91 ± 7	76 ± 5

TABLE 4.1

THE INTERACTION BETWEEN ALCOHOL (0.75G/KG) AND CONTAC 500: THE SIGNIFICANCE OF THE DIFFERENCES BETWEEN TREATMENT GROUPS (T-TESTS)

	A			B			C			D			E			F		
	(a) Alcohol + Contac 500 v (b) Alcohol			(a) Alcohol + Contac 500 v (b) Contac 500			(a) Alcohol + Contac 500 v (b) Placebo			(a) Alcohol v (b) Contac 500			(a) Alcohol v (b) Placebo			(a) Contac 500 v (b) Placebo		
Time (min) after alcohol drinking began	40	100	160	40	100	160	40	100	160	40	100	160	40	100	160	40	100	160
TEST																		
Manual dexterity	-	↑↑	-	↓↓↓	↓↓↓	↓↓↓	↓↓↓	↓↓↓	↓↓↓	↓↓↓	↓↓↓	↓↓↓	↓↓↓	↓↓↓	↓↓↓	-	-	-
Vienna Determination Apparatus																		
(a) correct responses	-	-	-	-	-	-	-	-	-	↓↓	-	-	↓↓	-	-	-	-	-
(b) errors	-	-	-	-	-	-	↓↓↓	-	-	-	-	-	↓↓↓	-	-	-	-	-
(c) estimated correct responses	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
(d) delayed correct responses	↑↑	-	-	-	-	-	-	-	-		-	-		-	-	-	-	-
Complex reaction time	-	-	-	-	↓↓↓	-	-	-	-	-	-	-	-	-	-	-	↑↑	-
Simple visual reaction time	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Simple auditory reaction time	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Numerical reasoning (correct responses)	-	-	-	↓↓	-	-	↓↓↓	-	-	-	-	-	↓↓	-	-	-	-	-
Numerical reasoning (errors)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Perceptual speed (correct answers)	-	-	-	↓↓↓	-	-	↓↓↓	↓↓↓	-	↓↓↓	-	-	↓↓	↓↓↓	-	-	-	-
Perceptual speed (errors)	-	-	-	-	-	-	↓↓	-	-	↓↓	-	-	-	-	-	-	-	-

↓↓ $P < 0.05$; ↓↓↓ $P < 0.01$

TABLE 4.2: INTERACTION BETWEEN ALCOHOL (0.75G/KG) AND CONTAC 500 (1 CAPSULE)

BLOOD ALCOHOL CONCENTRATION

Treatment	Mean Blood Alcohol Concentration (mg/100 ml) ± S.E. (n = 29)		
	Time (min)		
	40	100	160
Alcohol + Contac 500	92 ± 7	84 ± 5	64 ± 5
Alcohol + placebo	90 ± 6	83 ± 5	66 ± 6

TABLE 5.1

INTERACTION BETWEEN ALCOHOL (0.75 G/KG) AND ALLOPURINOL

BLOOD ALCOHOL CONCENTRATION

Drug Treatment	Blood Alcohol Concentration (mg/100 ml) Time (min)			
	40	100	160	
Alcohol + Allopurinol				
1st day (n = 8)	89 ± 10	74 ± 3	65 ± 2	
2nd day (n = 8)	102 ± 9	87 ± 2	73 ± 3	
Alcohol + Placebo				
1st day (n = 10)	89 ± 11	79 ± 4	66 ± 6	
2nd day (n - 10)	97 ± 9	91 ± 6	73 ± 6	

Significance Level $P < 0.05^{*}$ $P < 0.01^{**}$

TABLE 5.2

THE INTERACTION BETWEEN ALLOPURINOL AND ALCOHOL

TEST	COMPARISON (a) Alcohol + Allopurinol v (b) Alcohol + Placebo		
Time after Alcohol (min)	40	100	160
Standing steadiness (eyes open)	-	-	-
Standing steadiness (eyes closed)	↓↓	-	-
Complex reaction time	-	-	-
Simple visual reaction time	-	↓↓	↓↓
Simple auditory reaction time	-	-	↓↓
Manual dexterity	-	-	-
Numerical reasoning (correct answers)	-	↓↓	-
Numerical reasoning (errors)	-	-	-
Perceptual speed (correct answers)	-	-	-
Perceptual speed (errors)	-	↓↓	-
Vienna Determination Apparatus (correct responses)	-	-	-
Vienna Determination Apparatus (errors)	-	-	-
Vienna Determination Apparatus (delayed correct responses)	-	-	-
Vienna Determination Apparatus (estimated correct responses)	-	-	↓↓
Verbal fluency	-	-	↓↓

↑↑ = Performance of (a) better than (b); $P < 0.05$

↓↓ = Performance of (a) worse than (b);

TABLE 6.1

THE INTERACTION BETWEEN ALCOHOL (0.75 G/KG)
AND DISODIUM CROMOGLYCATE (40 MG).
THE EFFECT ON BLOOD ALCOHOL CONCENTRATION

(n = 17)

Drug Treatment			Blood Alcohol Concentration (mg/100 ml) ± S.E. Time (min)		
			40	100	160
Alcohol	+	DSCG	93 ± 8	85 ± 5	78 ± 5
Alcohol	+	Placebo	.91 ± 8	87 ± 6	76 ± 5

TABLE 6.2 DSCG EXPERIMENT

F-RATIOS FOR DIFFERENCES BETWEEN CORRECTED TREATMENT MEANS OBTAINED BY ANALYSIS OF COVARIANCE

Test	F-ratio (df = 3,44) Time (min)		
	40	100	160
Standing steadiness (eyes open)	8.580**	7.515**	3.572**
Standing steadiness (eyes closed)	11.149*	9.550**	2.790**
Simple visual reaction time	1.696	1.366	0.613
Simple auditory reaction time	4.282**	4.912**	2.044*
Complex reaction time	4.334**	4.339**	2.515**
Manual dexterity	10.251**	11.236**	1.933*
Numerical reasoning (correct answers)	3.389**	4.640**	1.080
Numerical reasoning (errors)	0.236	2.768**	1.521
Perceptual speed (errors)	1.251	2.425*	2.098*
Vienna determination apparatus (correct responses)	7.728**	6.029**	5.900**
Vienna determination apparatus (errors)	8.467**	6.181**	2.405*
Vienna determination apparatus (estimated correct responses)	5.789**	3.453**	3.991**

* $P < 0.05$

** $P < 0.01$

TABLE 6.3

THE INTERACTION BETWEEN ALCOHOL (0.75/KG) AND DISODIUM CROMOGLYCATE (40 MG): THE SIGNIFICANCE OF THE DIFFERENCE BETWEEN TREATMENTS GROUPS (T TESTS)

	COMPARISON																	
	A			B			C			D			E			F		
	(a) Alcohol + DSCG v (b) Alcohol			(a) Alcohol + DSCG v (b) DSCG			(a) Alcohol + DSCG v (b) Placebo			(a) Alcohol v (b) DSCG			(a) Alcohol v (b) Placebo			(a) DSCG v (b) Placebo		
Time (min) after alcohol drinking began	40	100	160	40	100	160	40	100	160	40	100	160	40	100	160	40	100	160
TEST																		
Standing steadiness (eyes open)	-	-	-	↓↓↓	↓↓↓	↓↓	↓↓↓	↓↓↓	-	↓↓↓	↓↓↓	↓↓	↓↓↓	↓↓↓	↓↓	-	-	-
Standing steadiness (eyes closed)	-	-	-	↓↓↓	↓↓↓	↓↓	↓↓↓	↓↓↓	↓↓	↓↓↓	↓↓↓	-	↓↓↓	↓↓↓	-	-	-	-
Manual dexterity	-	-	-	↓↓↓	↓↓↓	↓↓	↓↓↓	↓↓↓	-	↓↓↓	↓↓↓	-	↓↓↓	↓↓↓	-	-	-	-
Vienna Determination Apparatus																		
(a) correct responses	-	-	-	↓↓↓	↓↓↓	↓↓↓	↓↓↓	↓↓	↓↓↓	↓↓↓	↓↓↓	↓↓	↓↓↓	↓↓	-	-	-	-
(b) errors	-	-	-	↓↓↓	↓↓↓	↓↓↓	↓↓↓	↓↓↓	-	↓↓	↓↓↓	-	↓↓	↓↓	-	-	-	-
(c) estimated correct responses	-	-	-	↓↓↓	-	↓↓	↓↓↓	↓↓	↓↓	-	↓↓	↓↓	↓↓	↓↓	-	-	-	-
Complex reaction time	↑↑↑	-	-	-	↓↓	↓↓	-	↓↓↓	↓↓	↓↓↓	↓↓	-	↓↓	↓↓	-	-	-	-
Simple visual reaction time	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Simple auditory reaction time	-	-	-	↓↓	↓↓	-	↓↓↓	-	-	-	↓↓↓	↓↓	-	-	-	-	↑↑	-
Numerical reasoning (correct responses)	-	-	-	↓↓↓	↓↓↓	-	-	↓↓↓	-	↓↓	-	-	-	-	-	-	-	-
Numerical reasoning (errors)	-	-	-	-	-	-	-	-	↓↓↓	-	-	-	-	-	-	-	-	-
Perceptual speed (correct answers)	-	-	-	-	-	-	-	-	-	-	↓↓	↓↓	-	-	-	-	-	-
Perceptual speed (errors)	-	-	↑↑	-	↓↓	-	-	-	-	-	↓↓↓	↓↓↓	-	-	↓↓	-	↑↑	-

↓↓ $P < 0.05$; ↓↓↓ $P < 0.01$

APPENDIX 2

NOTES ON THE METHODS USED

PSYCHOMOTOR TESTS

(1) Standing Steadiness

The apparatus consisted of a platform beneath which is mounted a displacement transducer. Details of the platform are described elsewhere.[3] The actual movement of the platform on the vertical plane was less than 1 micron. The subject stands on the platform facing a cathode ray oscilloscope (Heathkit, Benton Harbour, Michigan, U.S.A. - Model 10-14) which can be used to display body sway and provide a visual cue for corrective movements. The subject was instructed to stand as still as he could without talking or moving his head. Any shift forwards or backwards created an electrical impulse which was amplified and recorded on a Grass Polygraph (Quincy, Mass., U.S.A.) . The impulses were integrated (Grass Integrator, Model P10B) to give an overall measure of body sway (frequency and amplitude) . A constant was set on the integrator and the time taken until the input reached this value was measured and termed epoch time. Body sway was measured under two conditions:

(i) eyes open

(ii) eyes closed.

(2) Simple and Complex Reaction Time

The timer used was the Vienna Reaction Apparatus (Schüfried, Stuttgart, West Germany). The subject sat with his finger poised over a 1 cm^2 response button and reacted to signals by pressing the button as quickly as possible. The signals consisted of red and white lights (2.5 cm in diameter, separated by a distance of 8 cm and

positioned 6.5 cm from the response button) and a sound (acoustic power 0.1 w, frequency response 1250 Hz) which were presented in programmed sequence. A timing device measured the interval between the appearance of the stimulus and the subject's response in msec. For simple visual and auditory reaction time, the subject was required to respond to a presentation of white light or the sound. For complex reaction time, he was to respond only when the white light and auditory stimulus occurred stimultaneously although the other stimuli, alone and in combination, were also presented. Subjects practised to a reasonable plateau of performance before control readings were recorded. In the experimental sessions, each subject responded to five visual, five auditory and five complex stimuli.

(3) Vienna Determination Apparatus

The Vienna Determination Apparatus (Schüfried, Stuttgart, West Germany) generates a sequence of visual and auditory stimuli and records button and foot pedal responses. The correct and incorrect responses to the signals were recorded. A correct response was registered when the appropriate response was made during the presentation of the signal. An incorrect response was registered when either an inappropriate response was made or when the subject failed to respond. In the experiment, the subject was required to respond to a series of 100 programmed signals of 0.95 sec duration. In addition, the subject was asked to estimate the number of correct responses he thought he had made.

COGNITIVE TESTS

(1) Numerical Reasoning

Two tests were used:

(a) A task based on the Australian Council for Educational Research (A.C.E.R.) Number Test. This is a simple multiplication task with 2-digit multiplicands. Parallel forms were prepared from tables of random numbers. A 1 min test period was used and two scores were recorded: number of correct answers and number of errors.

(b) The Arbeit und Konzentration Test Geräte (Zak, Simbach am Inn, West Germany). The subject was presented with a series of random single digit addition and subtraction displays and required to key in the answers by pressing one of the ten buttons situated just below the displays. Each response generated another display and the type of response, correct or incorrect, was automatically recorded. The subject was instructed to work as quickly as possible for 2 min and the number of correct and incorrect responses was recorded.

(2) Perceptual Speed

The task consisted of checking pairs of numbers, ranging from 3 to 12 digits and marking on a separate answer sheet whether they were the same or different. It was based on the A.C.E.R. Speed and Accuracy (number checking) Test. A number of parallel forms were used and the test period was 1 min. Two scores were taken: (i) number of correct answers and (ii) number of errors.

BIOCHEMICAL MEASUREMENTS

(1) Plasma Alcohol Concentrations

Plasma (1 ml) was placed in a stoppered 10 ml glass vial together with 1 ml of distilled water and 1 ml of isopropanol solution (1.6 mmol/l). After shaking, 2-3 µl was injected into a Hewlett Packard model 5750 gas liquid chromatograph. The ratios of the heights of the alcohol and isopropanol peaks were compared on a standard curve. The column was a 2 m stainless steeel helix 3.2 mm in diameter packed with Porapak Q (mesh 100-200). Operating temperatures were: column, 160°C; detector, 200°C; injection port, 200°C. Gas flows were: nitrogen carrier, 30 $ml.min^{-1}$; hydrogen, 30 $ml.min^{-1}$; air, 300 $ml.min^{-1}$.

(2) Blood Lactate Concentration

Whole blood (5 ml) was added to a centrifuge tube containing 5 ml of 1.22 mol/l trichloracetic acid in 0.5 mol/l HCl. After centrifugation (3,000 rev/min for 5 min), 0.1 ml of the clear supernatant was added to 0.7 ml of glycerine buffer (Varley, 1969) (adjusted to pH 9.0) in cuvettes. Nicotinamide adenine dinucleotide (NAD; 0.1 ml of 60.3 mmol/l) was added to the cuvettes which were fed into the LKB Rate Reaction Analyser. This instrument measures the rate of change in optical density induced by an enzyme-catalysed reaction involving NAD and NADH at 340 nm. Rabbit muscle crystalline lactic dehydrogenase (LDH; 0.1 ml of 80 units. ml^{-1}) was automatically injected and mixed with the sample and the increase in optical density was measured over 1 min. The rate of reaction was compared with those of standard solutions containing known concentrations of lactic acid.

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