Investigating drug–ethanol interactions

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1 Methodology developed in our laboratories for testing the interactive effects of ethanol and drugs on human psychomotor performance is discussed.

2 An attempt has been made to relate the findings of our studies to the results of real-life impairment, particularly in traffic crashes.

3 Proposals for more comprehensive testing of drug–ethanol interactions have been put forward which may increase the predictive value of such tests.

Keywords ethanol drugs human psychomotor performance

Introduction

Many drugs are capable of interacting with ethanol to modify the extent, the nature or the time-course of the impairment of psychomotor skills which might reasonably be expected from the ethanol dose administered. The descriptive terminology for drug–ethanol interactions is often confusing although a reasonable rationale to apply might be to consider a drug which shares some of its actions with ethanol as being potentially additive or supra-additive and one with a different mode of action as potentially antagonistic or synergistic. However, before the nature of a drug–ethanol interaction can be assessed, answers should be sought to the following questions:

(1) Is the time to peak psychomotor effect of either ethanol or the drug altered in the presence of the other?

(2) Does the magnitude of the peak blood concentration change for either the drug or ethanol in the presence of the other?

(3) Do the observed psychomotor effects parallel the blood concentration curves of either the drug or ethanol?

(4) Are the dose-response relationships for either drug altered in the presence of the other?

(5) Is the nature of the interaction consistent throughout the dose ranges and times of administration of the drug and ethanol?

Very few investigators, including ourselves, have attempted to answer more than one or two

of these questions for a given interaction, although it is now very clear that if the results of such studies are to be of any predictive value for real-life impairment of patients receiving drug therapy and consuming 'social' amounts of ethanol, a much more comprehensive approach needs to be adopted.

In this paper, the development of the test battery which we currently use for the investigation of drug–ethanol interactions will be discussed and some of the results we have obtained will be presented. The approach was essentially to find a series of tests which were sensitive to the effects of ethanol in a dose-dependent manner and then to administer other drugs and to observe how the response pattern was modified. The relevance of the results of these tests to real driving or other skills performed has not as yet been established.

Methods

Subjects

Subjects in our experiments are invariably young, healthy, paid (usually University student) volunteers. They are medically examined (including blood biochemistry and haematology) to ensure that no past or present illness precludes their participation in the experiment.

A 'drugs and medication' questionnaire is administered and, in some cases (cannabis experiments), subjects are required to state that they are not naive to the drug under test. The purpose of the experiment is fully explained to them and their informed consent is obtained.

Ethanol

To avoid possible modification of the ethanol effect (Greizerstein, 1981) by the cogeners which are present in all alcoholic beverages (with the possible exception of vodka), it has been our practice to use pure ethanol (rectified spirit BP) diluted to 10 or 20% v/v in sugar-free lemon cordial. This is consumed at a constant rate under close supervision and produces a peak blood ethanol concentration in fasted subjects about 20 min after finishing the dose. The placebo, ethanol-free lemon cordial is not an effective one. More recently, we have devised a placebo ethanol preparation (Perl *et al.*, in preparation) consisting of unsweetened orange juice to which is added 2% concentrated peppermint water BP, which is not only successful in disguising the presence of ethanol in triangular tasting tests but shows a small effect in the results of the psychomotor tests (Table 1). The ethanol dose is taken ice-cold through a short plastic tube; the stopper of the container is a thimble filled with pure ethanol providing olfactory masking. Our fears that the sugars in the orange juice would delay the absorption of ethanol were not realised, perhaps because of the carminative effect of the peppermint. Even with high doses of ethanol (> 1.0 g/kg), consumed over a short period, the subjects do not complain of nausea.

Table 1 Mean scores for replies to the question 'have you received alcohol today?' (scaled yes = 1, no = 0). The experiment was carried out to investigate the interactive effects of two analgesics with ethanol on a double blind basis ($n = 12$; in which there were three ethanol and three placebo ethanol treatments (Bird *et al.*, in preparation).

	Placebo ethanol	Ethanol
Analgesic 1	0.42	1.00
Analgesic 2	0.67	1.00
Placebo drug	0.33	1.00

Drugs

Normally in our experiments, single mid-range therapeutic doses of prescribed drugs have been

used. Placebo dose-forms were thus readily available. The same considerations applied to orally-administered cannabinoids which were dissolved in sesame oil and sealed into capsules (Belgrave *et al.*, 1979). Placebo capsules contained only sesame oil. Cannabis for smoking was prepared by extraction of the cannabinoids with ethanol (< 0.003% THC). Placebo cigarettes were made from this material. Active cigarettes were prepared by addition along the length of the cigarette of a measured dose of cannabinoid(s) by means of a microsyringe and a long needle. The cigarettes were humidified for 24 h before use (Chesler & Starmer, 1983).

The test battery

When these studies were commenced, a battery of tests was designed to obtain as broad a coverage as possible of perceptual, motor and intellectual functions which had been reported to be sensitive to the effects of ethanol (Wallgren & Barry, 1970) and are described in detail elsewhere (Franks *et al.*, 1976, 1977). One overriding consideration was that the whole test battery could be completed within 20 min in order to follow a rapidly changing blood ethanol concentration. The tests which have been used include:

- (1) *Standing steadiness* The subject stands on a platform beneath which a displacement transducer is mounted, the output of the transducer which results from any shift in position creates an electrical impulse which is amplified and integrated to give an overall measure of body sway (frequency and amplitude). Measurements are made with the eyes open, with or without a visual cue, and with the eyes closed. A hand steadiness test is also used.
- (2) *Simple and complex reaction time* Response times to the presentation of simple visual and auditory stimuli are measured and also when a particular stimulus combination has to be selected from a number of alternatives.
- (3) *Pursuit rotor* This is essentially a hand-arm co-ordination test. The subject is required to track a light which moves round a circular track with a photocell stylus. The number of times the stylus goes off target and the dwell time off-target are recorded.
- (4) *The Vienna determination apparatus* This test involves responding appropriately on one of nine possible responses for nine appropriately matched single mode stimuli (five coloured light stimuli and five similarly coloured buttons to press, high and low tones

and named buttons and left and right foot pedals for appropriate signal lights). One hundred randomised signals (1.22 s duration) are presented and correct, incorrect and delayed responses are recorded.

(5) *Numerical reasoning* Two tests have been used; a simple multiplication of two-digit multiplicands and addition and subtraction *via* key press to a display of single digit numbers. This is regarded as a speeded number test because of the reaction time component.

(6) *Manual dexterity* This test involves the transference of small metal bolts to a line of holes in a vertical work-plate and the completion time is recorded.

(7) *Divided attention task* Here, the subject has to attend to a light source changing in colour and also to three boards of lights (nine in the middle board and 6 in each side board set at an angle of 135 degrees from the middle board). The number of critical responses can be varied to create either a high- or a low-demand situation and there is provision for error feedback.

(8) *Perceptual speed* Checking pairs of numbers and responding whether they were the same or different was used in some of the early studies.

(9) *The Sternberg paradigm* This is a test of the speed of information processing and measures the time taken to recognise items in relatively short (1–6) lists of numbers. Sternberg (1966, 1969), found that the reaction time increased linearly with the length of the list.

(10) *Pen and paper tests* Occasionally, pen and paper tests such as the letter sets test (Thurstone, 1938), an inference test (Guildford, 1962), the cubes comparison test (Thurstone, 1962) and a word construction test have been used.

(11) *Mood scales* Subjective intoxication ratings are assessed on a monopolar 0 to 10 analogue scale, a score of 0 indicating there to be no discernible drug effect and 10 being 'as drunk as I have ever been'. No access to previous assessments is allowed when filling in the scale. Questions are also asked about willingness to drive a motor vehicle.

Blood ethanol concentrations

Blood ethanol concentrations are measured either directly by gas-liquid chromatography from 100 μ l fingertip samples or by breath analysis using either a gas chromatograph (Intoximeter) or an infra-red instrument (In-

toxilyzer). In the latter case, precautions must be taken to prevent the interference of mouth ethanol and this precludes some measurements on the rising limb of the blood ethanol curve.

Procedure

The subjects arrive at the laboratory not less than 2 h after consuming a light non-fatty breakfast. They are subjected to breath analysis to ensure that they are ethanol-free and then they are practised to a reasonable plateau of performance before drugs are administered. Most of our studies, to date, have involved the administration of single mid-range therapeutic doses of drugs and, in general, plasma blood concentrations have not been monitored. In the first instance, in order to maximise the chances of detecting a psychomotor performance rather than an absorptive interaction, the times of administration of the drug and ethanol are arranged so that they might be expected to attain maximum plasma concentration at about the same time.

Analysis of data

In the early experiments, an analysis of covariance was used with the pre-drug values as the co-variate for performance on subsequent tests. Such an approach has many deficiencies. The experimental designs used in these studies involve several times of measurement (at least four) and several variates or performance measures (typically, about 10). In order to avoid an unacceptable inflation of the Type 1 error rate (such as would result from a series of *t*-tests on pairwise comparisons on individual variates), analyses have been carried out using simultaneous test procedures (Bird, 1975) which control the probability of one or more Type 1 errors in a set of tests, such as, for example, all tests within a particular main effect or a particular interaction effect.

If the Type 1 error rate refers to the set of tests within a particular effect in a multivariate experiment, three main approaches can be considered.

(1) The analysis can consist of a set of univariate analyses (say ANOVAs), one univariate analysis per variate, with the Type 1 error rate per analysis set at α/P , where P is the number of variates. This Bonferroni adjustment to univariate tests produces acceptable control over the Type 1 error rate, but at the cost of conservative tests on individual measures (if $P = 10$, a test would

require a *P* figure of less than 0.005 before significance could be claimed at the 0.05 level).

(2) A multivariate analysis of variance (MANOVA) could be carried out. This procedure does consider all variates simultaneously, and it defines linear combinations (discriminant functions) which maximize the site of a particular effect. Discriminant functions can be difficult to interpret, however, and in some situations (those where the number of subjects does not exceed the number of tests by a very large margin), MANOVA tests on individual measures or on linear combinations other than discriminant functions can be extremely conservative. In our situation, MANOVA analysis strategy would be inappropriate for this reason.

(3) An analysis can be based on multivariate methods of data reduction (such as principal components analysis (PCA) or, more generally, factor analysis (FA) which reduce the dimensionality of the data (i.e. the number of factors is smaller than the number of variates), without (hopefully) losing much information about the effects of interest (drug effects etc). If the data reduction is successful in this sense, then Bonferroni-adjusted tests can be used to good effect, because the adjustment has less effect due to the reduction in the number of tests. Factor scores are, in general, more reliable than the variates on which they are based, and (after rotation if necessary) usually easier to interpret than discriminant functions.

Our experiences from a series of drug studies using the same test battery suggest that an analysis strategy using Bonferroni-adjusted tests on factor scores is more suitable than either of the other strategies given the number of subjects and the type of experimental design which we typically use. *F* ratios for testing hypotheses of interest are usually at least as high as for the most sensitive of the individual measures, the data is generally less noisy than for typical individual measures, and simultaneous tests are less conservative than when applied to individual measures.

Results

Ethanol alone

In our first attempt to demonstrate the effects of ethanol on performance in the test battery (Franks *et al.*, 1976), three doses of ethanol (0.54, 0.75 and 1.0 g/kg) and a placebo were administered to 12 subjects according to a 4×4

crossover design. In general, ethanol induced a dose-dependent decrement in the performance on all tests. However, although there were significant differences in the blood ethanol concentrations attained after the intermediate and low doses of ethanol, the differences in performance were not very pronounced. Of the tests employed, body sway appeared to be the most sensitive to the effects of ethanol followed by reaction speed and manual dexterity. Like Goldberg (1943), it was found that cognitive functions were less affected by ethanol than motor functions and recovered sooner. More recently, the question of dose-dependence for ethanol-induced performance decrement across the test battery has been re-examined (Stramarcos & Chesher, in preparation), as part of a comparison of the effects of ethanol and tetrahydrocannabinol on human skills performance and mood. Five doses of ethanol were used (0, 0.30, 0.54, 0.75 and 1.0 g/kg) and 15 subjects were assigned to each dose-group. It was again shown that ethanol impaired performance across the test battery in a dose-dependent manner. There were, however, some differences in the relative effects of ethanol on individual tests and this requires further examination. There was also a dose-dependent mood effect of ethanol across time and peak intoxication ratings closely followed the peak blood ethanol concentrations attained. Interestingly, placebo-treated subjects reported appreciable mood effects which were not distinguishable from those of the lowest ethanol dose. The divided attention task has never been incorporated into the test battery proper, largely because of the length of time necessary to complete it. Preliminary results (Job *et al.*, 1983) have indicated that ethanol (0.75 g/kg) induced significant performance deficits with the apparatus in a high-demand mode. Specifically, after ethanol, subjects made less responses overall in both components of the test and more stimuli were missed but there was no increase in the false alarm rate.

Acute tolerance to the effects of ethanol on performance in this test battery (Table 2) was found to occur (Lind *et al.*, 1983). Subjects were tested (on two occasions) at 50 or 90 min after receiving an ethanol dose (1.0 g/kg, as a 20% v/v solution consumed over 30 min) when the mean blood ethanol concentrations were not significantly different. Similar effects were also seen in an experiment designed to investigate the supposed antagonism of ethanol impairment by naloxone (Bird *et al.*, 1982).

We have carried out a twin study of susceptibility to ethanol intoxication in which 206 twin-pairs were tested before and after the adminis-

tration of a standard dose-of ethanol (0.75 g/kg). Repeat measurements were obtained for 41 of these pairs on a second occasion and some of the early results have been reported (Martin *et al.*, 1981). It was found that females attained significantly higher blood and breath ethanol concentrations than males, which could not be accounted for in terms of adiposity, weight or lung volume and the physiological basis of this effect remains unclear.

Significant performance decrements occurred in all tests after ethanol administration and a principal components analysis revealed that the tests measured different skills. In the body sway task, the performance of females deteriorated much more than that of males even after correction for height and weight. A similar effect was noted in the results of the pursuit rotor test. Performance after ethanol in some tests, notably the Vienna determination apparatus, revealed a sex-related trade-off in the response. Males tended to make more incorrect responses while in the females, the number of delayed correct responses was increased, perhaps reflecting greater caution under the influence of ethanol. The actual blood ethanol concentrations attained and pre-

vious drinking experience were found to be poor predictors of the deterioration in individual performance which occurred after ethanol.

Ethanol and drugs

A number of findings are of interest in this context. For example, the interactive effects of some benzodiazepines with ethanol appear to be much more marked than those of others. Whereas in most tests (Franks, 1974), there was evidence for an interactive effect, apparently greater than additivity, between ethanol (0.54 and 0.75 g/kg) and diazepam (5 and 10 mg/kg), when chlordiazepoxide (20 and 40 mg/kg) was given together with the same doses of ethanol no such pattern emerged and in some cases there were trends towards antagonism. This type of antagonistic activity has also been reported by others (e.g. Goldberg, 1966; Dundee & Isaac, 1971).

A series of studies has been carried out on the effects of histamine H₁-receptor antagonists on psychomotor performance, alone and when combined with ethanol. These also revealed a

Table 2 Comparison of the performance of ethanol-treated (1.0 g/kg) subjects when tested at 50 and 90 min after drinking began (*n* = 30).

<i>Test</i>	<i>Z</i> (1)	<i>P</i> (2)	<i>Performance</i>
Standing steadiness eyes open	-4.671	< 0.001	T90 > T50
Standing steadiness eyes closed	-2.979	< 0.003	T90 > T50
Pursuit rotor target error	-3.887	< 0.001	T90 < T50
Pursuit rotor time error	-3.445	< 0.001	T90 < T50
Numerical reasoning Number correct	-2.119	< 0.034	T90 > T50
Numerical reasoning Number of errors	-2.846	< 0.004	T90 < T50
Perceptual orientation Number correct	-2.184	< 0.029	T90 > T50
Perceptual orientation Number of errors	-2.847	< 0.004	T90 < T50

(1) *Z* = normal distribution approximation to the Wilcoxon statistic.

(2) *P* = two-tailed.

gradation of effects ranging from impairment when diphenhydramine and promethazine were given alone (Belgrave *et al.*, unpublished observations) through either considerable or slight ethanol-interactive effects with dexchlorpheniramine (Franks *et al.*, 1978) and mebhydrolin (Franks *et al.*, 1981) to no evidence for any interaction with clemastine (Franks *et al.*, 1979). It was also shown that disodium cromoglycate, which is also used for the treatment of allergic rhinitis, has no adverse effects on performance when given alone and did not interact with ethanol (Crawford *et al.*, 1976).

For a number of years, we have been concerned with the interactive effects of cannabinoids (particularly tetrahydrocannabinol) with ethanol. In most of the studies completed to date, the cannabinoids were given orally although, as mentioned earlier, we have developed a timed smoking technique which appears to give reproducible results (Chesher & Starmer, 1983). These studies have indicated that both tetrahydrocannabinol (THC; 10, 15 and 20 mg/70 kg) and ethanol (0.54 g/kg) produce a decrement of performance on the battery of tests (Chesher *et al.*, 1976, 1977; Belgrave *et al.*, 1979). The interactive effect increased with the dose of THC. In another experiment, all of the possible combinations of THC (214 µg/kg), cannabidiol, CBD (286 µg/kg), cannabinol, CBN (286 µg/kg) and ethanol (0.54 g/kg) were administered and performance was assessed. Both THC and ethanol produced significant performance decrements and their combined effects were described in terms of an additive model. There was no suggestion of any effects produced by CBD or CBN in the doses used nor was there any evidence that these substances modified the effects of either THC or ethanol (Bird *et al.*, 1980).

In a number of instances we have been asked to evaluate the efficacy of various sugar-based preparations which are sold to reduce blood ethanol concentrations and, by implication, the extent of the ensuing inebriation. High doses of both fructose and dextrose (1.2 g/kg) administered by mouth 40 min after the consumption of ethanol (1.0 g/kg), significantly reduced the peak blood ethanol concentrations attained, probably by increasing gastric emptying time, and there was a commensurate reduction in psychomotor impairment. No increase in the rate of disappearance of ethanol from the blood could be demonstrated, however (Franks *et al.*, 1977). A small but significant increase in the rate of ethanol metabolism was demonstrated, however, when fructose was administered at the beginning of the ethanol-elimination phase (Perl & Starmer, in preparation) but the

behavioural consequences of this effect remain to be established. A study of the interactive effects of caffeine (300 mg/70 kg) and a 0.75 g/kg dose of ethanol (Franks *et al.*, 1975) revealed that caffeine only antagonised the ethanol-induced decrements in performance on the reaction time tests; other performance deficits were either unaffected or insignificantly increased by caffeine.

The question of drug-induced blockade of the development of acute tolerance to ethanol should also be considered as a special type of drug-ethanol interaction. In animal experiments, it was shown that drugs which interfere with the actions of catecholamines in the CNS, notably α -adrenoceptor antagonists, prevented the development of acute tolerance to ethanol (Edwards *et al.*, 1983).

Discussion

We have carried out studies of drug-ethanol interactions for a number of reasons including epidemiological evidence for increased crash-risk (e.g. Bird *et al.*, 1980; MacPherson *et al.*, 1984), where preparations are suggested to ameliorate the inebriant effects of ethanol (Franks *et al.*, 1977; Perl & Starmer, 1983) or to make comparisons among drugs which are used for essentially the same therapeutic purposes (Franks *et al.*, 1978, 1981).

Young, healthy volunteers, who may not constitute an appropriate test population, have been used but, at least, the effects of illness or disability on psychomotor performance were absent as a confounding factor and, arguably, this may be a reasonable point to start an investigation. We have seldom carried out sub-chronic studies on drug-ethanol interactions. The fact that the results of single-dose studies can be quite misleading can be gained from a comparison of our findings for caffeine and ethanol (Franks *et al.*, 1975), where an incomplete antagonism was found, with those of Moskowitz & Burns (1980) and Lee & Lowe (1980) who found the effects of ethanol to be exacerbated by ethanol under certain conditions. We are currently conducting a multi-dose study of caffeine-ethanol interaction.

The results we have obtained to date indicate that we can reliably detect ethanol-induced impairment in *groups* of individuals at blood ethanol concentrations as low as 0.05 g/100 ml. In some tests, notably the body sway task, the detection threshold is even lower. This should not, however, in our experience, be extended to a prediction of the degree of impairment

likely to be exhibited by a given individual who receives a standard dose of ethanol, both because of variations in the blood ethanol concentrations attained and in the extent of the psychomotor deficit induced. About half of the variation in the peak blood ethanol concentration reached is repeatable between occasions and only a small proportion of the non-repeatable variance is explicable in terms of measurement error or drinking experience (Martin *et al.* in preparation). Where blood ethanol concentrations are measured by breath analysis, a more realistic mean blood-breath partition ratio was found to be 1:2286 rather than the 1:2100 ratio at which most commercial instruments are calibrated. For a number of evidential instruments, regression equations have been calculated to predict the blood ethanol concentrations from any given reading and to estimate the accuracy of the prediction (Perl *et al.*, in preparation).

There is an understandable tendency to attempt to extrapolate the results of tests of drug effects on the performance of healthy volunteers in laboratory tasks to patients in real life situations, who operate machinery, work in a hazardous environment and (particularly) drive motor vehicles where harsh penalties for drug-impairment often exist. Driving is a multi-functional task which includes visual search and recognition, vigilance, information processing under variable load, risk-taking, decision-making and sensorimotor control. In our current state of knowledge, psychomotor test procedures, at best, attempt to sample elements of these skills on the basis that they are simple, safe and repeatable and the results can be related to drug concentrations in body fluids.

Some of the tests which we use have face-validity for driving skills such as the reaction time, pursuit rotor, the motor co-ordination and divided attention tasks. If the speeded number test is regarded as one of work and attention, then a case may be made for its relevance also. The body sway task is difficult to justify in the present context and its continued presence in the battery derives from its sensitivity to both ethanol and cannabis intoxication and also to stimulants, such as caffeine.

Our test battery, we believe, concentrates far too heavily on sensorimotor skills and, at present, we are examining tests which measure various aspects of information processing since it is this aspect of driving ability which now appears to be most affected by drugs rather than peripheral sensory input or motor control mechanisms. The tests under development include complex counting and continuous short-term memory tasks. The important parameters

appear to be speed of information processing and maintenance of concentration and the comparative effect of memory load under the influence of drugs. Our experience with the Sternberg test has been confined to showing that marked differences in the rate of information processing exist in alcoholics compared with a matched population of total abstainers (Nikias & Chesher, in preparation) and we have not examined the acute effects of either ethanol or drugs as yet.

There have been few attempts to examine the relationship between the effects of drugs on laboratory tasks and real driving performance. De Gier *et al.* (1981) compared psychomotor performance and real driving performance in patients stabilised on diazepam. Driving ability and performance in a low-demand laboratory task were found to be impaired but there was no significant performance deficit in a high-demand situation. Linnoila's group (personal communication, 1981) found a negative correlation to exist between the psychomotor performance of bus drivers and their accident records. Sometimes, similar results have been obtained in laboratory and real driving tasks such as the finding of an additive interaction for ethanol and tetrahydrocannabinol by Attwood *et al.* (1981) and ourselves (Bird *et al.*, 1981). In an attempt to cross-correlate performance on the test battery with real driving, we are shortly commencing a study using police drivers with two levels of experience (recruit and highway patrol), who will receive three ethanol treatments (0, 0.54 and 0.75 g/kg) and be tested in the laboratory and on a closed track where performance can be scored.

For the last few years, we have examined self-reported drug usage in drivers subjected to evidential breath analysis in New South Wales and related this to the age and sex of the driver and to whether or not breath analysis occurred after a crash (MacPherson *et al.*, 1984). A log-linear analysis was carried out on the cross-tabulation of age (five categories) by blood ethanol concentration (five categories) by drug (13 categories) by crash/no crash. A reduced model was obtained, and the ratio of the odds of a crash in each drug group to the odds of a crash in the appropriate drug-negative group was computed. In a second stage of the analysis, the analgesic and CNS depressant categories were expanded to individual agents and odds ratios again computed. A number of individual drugs and drug groups were associated with an elevated chance of being breath analysed as a result of a crash. These included CNS depressants (diazepam, oxazepam, anti-depressants), analgesics (dextropropoxyphene)

and sulphonylureas. It is interesting to note that there were no pharmacological surprises in the data and, in general, these effects were most marked at low blood ethanol concentrations. The results of this study are seen as a means of ordering priorities for research and the methodology has been extended to the roadside breath screening situation where much more information is available on mode of apprehension and culpability. In a pilot study, we have analysed the blood of drivers admitted to a Sydney hospital as a result of a crash for the presence of ethanol, total cannabinoids and THC (Chesher & Starmer, 1983). A total of 130 samples have been collected. Of these, 36 (28%) were positive for ethanol, 29 of these had blood ethanol concentrations greater than 0.05 g/100 ml (the legal limit) and 16 in excess of 0.08 g/100 ml. Of the total sample, 104 have been analysed for cannabinoids and 23% were positive with one third of them having detectable levels of THC. Of the seven positive THC cases, three were also positive for ethanol. This work is proceeding and will be extended to other drugs now that blood sampling is mandatory for drivers admitted to hospital as a result of a crash.

One practical problem in these studies which has never been really resolved is the question of the effects of the withdrawal of blood samples during the course of the experiment, either with the use of an in-dwelling catheter or by repeated venepunctures, on the performance of subjects in the psychomotor tests. Blood ethanol concentrations, when measured by breath analysis or from fingertip blood samples appear to cause no problems but where serial blood sampling is necessary, we consider that the two activities should be separated. Another problem is tobacco smoking or the abstinence therefrom. We always attempt to recruit non-smokers but sometimes (especially in the cannabis experiments) this is virtually impossible. Despite the fact that it has been reported (Leigh *et al.*, 1977) that heavy smoking can confound the effects of ethanol in a divided attention task), we have considered that the disruptive effects of acute nicotine withdrawal on performance would probably be greater. We therefore allow such subjects to smoke minimally during the testing sessions. Clearly, this problem needs further investigation.

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In future, the drug-ethanol interaction studies we propose to carry out will consist of two acute and one sub-chronic experiment for each test drug. In the first acute experiment, subjects will attend the laboratory on five occasions, the first for medical examination and practice to plateau on each of the selected tests. On the remaining four occasions, they will receive four treatments on a random double-blind basis consisting of a placebo and three doses of the drug within the accepted therapeutic or social range. On these occasions, subjects will be cannulated *via* a forearm vein for collection of blood samples. Mood scales will be administered before each blood sample is taken and only one, or at most two, performance tests will be used. In the second phase of the study, a much larger number of subjects will be used but after the practice session they will only attend the laboratory on one occasion and receive only one dose of the test drug. Here, the full test performance battery will be administered but only one or two blood samples will be withdrawn for analysis on a random basis for comparison with the pharmacokinetic data. It has become apparent (Linnoila, personal communication, 1981) that psychomotor and cognitive impairment induced by psychoactive drugs is most prominent during the first few weeks of therapy. It is therefore proposed to use two doses of the test drug, chosen on the basis of experience in the first two experiments. Performance deficits and mood changes will be measured after the first and twenty-second doses. Compliance will be checked by random urine analysis. When this information is available it should be possible to combine several doses of the drug and of ethanol and to determine whether substantial changes occur either in the pharmacokinetic parameters or in the behavioural effects of the drug-ethanol combination. Comprehensive studies, such as have been proposed are commonplace in other areas of medical research and it is difficult to put forward reasons, other than cost, why they should not be applied to a drug-ethanol interaction study if problems can be shown to exist or are suspected and to advise physicians of differences within a class of drugs used for essentially the same purposes.

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