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*Phil. Trans. R. Soc. Lond. B* 1990 **327**, 513-518  
doi: 10.1098/rstb.1990.0094

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## Medication and skilled work

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There is increasing interest in the way in which drugs impair performance. This has arisen because some may impair day-to-day skills of those whose occupations demand vigilance and motor skill, and of those who are involved in decision making or where interpersonal relations are crucial. For many years the position was adopted, at least in certain occupations where impaired performance could be a danger to others, that the use of any drug should preclude employment. However, recent advances in therapeutics and a greater understanding of drug action in man has made this rather uncomplicated view of life less tenable, and there is now an increasing desire that advances in therapy should, if at all possible, be available to occupational groups, such as airline pilots. In this way the adverse effect which a drug may have on performance has become an important aspect of its clinical profile.

Hypnotics appropriate for transient insomnia, which may arise from the irregularity of rest inherent in many occupations, need to be free of residual effects, antihistamines that are sedative must be avoided, and drugs used in the management of mild hypertension, often during the important years of middle life, must be as free as possible from central effects. And it must be emphasized that these drugs are often used by active, healthy or near healthy individuals. The issues involved in the safe use of a particular drug by a particular individual are complex, and as with all aspects of therapeutics it is sometimes necessary to balance efficacy and adverse effects.

### INTRODUCTION

The purpose of this paper is to discuss the issues involved in making the decision of whether a certain drug or drugs can be used safely. Hypnotics and antihistamines present examples of the two main problems which arise. In the case of antihistamines, whether individuals can work safely under the influence of a drug, and in the case of hypnotics, how long after ingestion of a drug that is known to impair performance it is safe to carry out skilled work. The aim is to show the current approach to the safe use of drugs, and to outline the ways that may be adopted to ensure that a drug can be used by those involved in skilled work.

### METHODOLOGY

Broadly speaking, there are two approaches to the study of performance, and also for predicting the effect that a drug has on the day-to-day life of an individual. The activity of a drug can be built up as a profile by using a variety of laboratory tests directed to assessing specific skills relevant to the work of the individual, or the skill itself may be simulated with as much accuracy as possible. In the two approaches there are common considerations of methodology.

In all such studies dose- and time-response data are needed, and the dose range must be relevant to the projected therapeutic use. In the case of centrally acting drugs it may be appropriate to include a dose which, though outside the anticipated therapeutic range, is high

enough to impair performance, as this would give an indication of the margin of safety. Dose- and time-related studies have the advantage that the analysis of the data is more likely to detect a relevant effect than analysis of single assessments, and that variations in performance related to the circadian activity of the individual are taken into account. Measurements must, of course, be related to ingestion of placebo, and an active control should be used to ensure that absence of impaired performance is not due to relative insensitivity of the testing procedures.

A large variety of tests has been used in the assessment of impaired performance. These include the deceptively simple paper and pencil tests, such as digit symbol substitution, tests that assess memory and attention, and those that assess psychomotor skill. Tests are also used which relate to specific senses such as vision. Those which measure a neurological entity such as body sway, eye movement, flicker fusion, electrical activity of the brain, and more recently, drowsiness (sleep latencies during the day), are also included. These avoid the problems of measuring performance, and so may be useful when there are difficulties in measuring performance, as in the elderly. However, more needs to be known about the significance of changes in such functions to the overall capability of the individual before they can be used alone in the study of impaired performance with drugs.

As to the choice of tests there are two main issues: information on the skill impaired and on the persistence of effect (evidence of modified central activity) is needed. If information on persistence of effect is sought, no matter how minimal, accurate and well-designed studies with pencil and paper are often useful. Psychomotor skills related to the peripheral nervous or oculomotor systems are sensitive tests of skill impairment.

Inevitably the question arises concerning the relevance of performance tests carried out in the laboratory to the day-to-day work of the individual. Many laboratory tasks such as reaction time, pursuit rotor, motor coordination and divided attention may have mere face validity (Starmer & Bird 1984). The study of perception and cognition has been specially advocated (Moskowitz 1984) because the majority of driver-related errors fall into the category of information failures, and attention is the most frequently cited area in alcohol-related accidents. At a first look simulation would appear to be a more attractive approach, but there are serious concerns whether simulation is particularly relevant to the real situation. Indeed, it must be questioned whether studies using simulators are as useful as laboratory tests in providing reliable information on drug effects.

#### SIMULATION

Simulation of an occupation or of a day-to-day skill may bring increased reality and motivation to the participation of the subject, but it may nevertheless lack sensitivity in the measurement of performance itself. In a recent study, an antihistamine failed to impair driving performance, whereas it impaired performance on an adaptive tracking task (Cohen *et al.* 1984). The sensitivity of a simulation to centrally acting drugs must always be established. An absence of an effect is of limited value unless it is known at what dose of that drug, or a similar drug, performance would be impaired. Similarly, information on efficacy and adverse effects spread over the whole of the therapeutic dose range is needed. Dose- and time-response data, as in all studies with drugs, are essential.

Clearly, uncertain or insensitive measures obtained with simulation have no advantage over accurate measures from the laboratory. It must be realised that simulators (including vehicle

handling tests) are often testing isolated functions in a complex, expensive and uncontrolled way. As pointed out (Starmer & Bird 1984), driving includes the skills of visual search and recognition, information processing under variable load, risk taking, decision making and motor control. There are many factors that influence measurement in a complex situation, and these, together with the inherent variability of a situation that involves simulation, can lead to difficulties in establishing a drug effect.

It is important that a spurious confidence in the use of simulation and in vehicle handling tests does not arise. As far as car accidents are concerned, they are only seldom related to loss of control. It may be far more important to study the decision as to whether a specific manoeuvre is thought to be possible than the ability to carry out accurately the manoeuvre itself, and to study the ability to cope with an unexpected situation than the skill involved in negotiating stationary obstacles. The studies of Cohen (1966) and of Brown *et al.* (1969) have shown that the number of times a vehicle may be driven successfully through a gap of any particular size may not be affected by alcohol, but the inebriated driver attempts more gaps smaller than the size of the vehicle. Further, as pointed out by Walsh (1984), though drugs may only impair well-learned behaviour at high doses, they may impair coping or learning skills at low doses, and this is clearly relevant to the ability to cope with mechanical failure or if someone runs in front of a car.

There are other considerations that must also be borne in mind. A simple handling experiment does not represent the complexity of driving experience, different skills are needed for different types of driving, and an immediate transfer of experience between simulated driving and real driving is unlikely to exist. Personality may also have an important part to play in the genesis of accidents. Reaction times are faster in young people but slower in the elderly, yet accident incidence is the other way around. It is also essential that the more subtle effects of drugs on man are borne in mind. Effects on decision making and on the behavioural integrality of man have yet to be adequately explored, and the impairment of such complex skills may be of considerable significance to the individual.

Cohen *et al.* (1984) have pointed out that, though impairment of real or 'off road' driving has been produced by moderate to large doses of benzodiazepines (Zezulka & Wright 1982), barbiturates and major tranquillizers (Betts *et al.* 1972), antihistamines and lower doses of benzodiazepines sufficient to cause sedation in patients and volunteers (Peck *et al.* 1975) have failed to impair driving performance (O'Hanlon *et al.* 1982; Hindmarch 1976). We must, therefore, always question whether failure to demonstrate impaired vehicle handling means that a drug is unlikely to impair driving or cause accidents.

Nevertheless, there is some measure of agreement between careful studies that use simulation and similar studies with laboratory tests. It is the contention that laboratory tests do not provide such useful information as simulation or vehicle handling that causes most dispute. Laboratory tests can measure skills that need to be preserved and which, in the case of accidents, may be identified from epidemiological studies, but with simulation, careful assessment of its relation to the overall task in question is needed. There is a need to integrate data from different methodologies, and it would be useful if a simple test that has been used widely in studies on the central effects of drugs was included in all studies. Information with a relatively simple task known to be sensitive to centrally acting drugs, such as digit symbol substitution, would allow comparative information to be built up between centres that use laboratory tests and simulation. For the moment, laboratory tests are preferred for the analysis

of drug effects, as they provide reliable information on the nature of the skill impaired and on persistence of the effect of a drug (Broadbent 1984).

#### CLINICAL PHARMACOLOGY

The approach used to explore the effects of a drug on performance must relate to the way in which it is to be used. It may be relevant to establish the residual effects of a drug, or it may be important to establish whether it is safe to work while the drug is acting. If persistence of activity is the issue (and hypnotics are a useful example as they are used overnight), the question is whether it is safe to carry out skilled work the next day. Duration of action depends on absorption, distribution into the tissues and elimination not only of the parent drug, but also of its metabolites, and consideration of both pharmacokinetic data and pharmacodynamic studies is necessary before recommendations that relate to safe use can be made with confidence. For instance, the pharmacokinetic profile and pharmacodynamic effects are essential to define accurately the likelihood of residual daytime impairment (Nicholson 1986).

Although hypnotics may be used safely as long as their effect does not persist beyond the sleep period, many drugs are used during the period of work itself, and so may easily affect performance. An example is the antihistamines that are used for their peripheral anti-allergic properties, though they often lead to drowsiness and impaired performance (Nicholson 1983). Drowsiness with the H<sub>1</sub>-antihistamines has been attributed to various mechanisms such as inhibition of histamine *N*-methyltransferase and blockade of central histaminergic receptors, though serotonergic antagonism, anticholinergic activity and blockade of central alpha adrenoceptors may also be involved.

Whatever may be the cause of sedation with antihistamines the central effects are dependent on the ability of a particular drug to cross the blood–brain barrier, and may pass with ease. The solution would be to develop antihistamines that have difficulty in crossing the blood–brain barrier. Indeed, such antihistamines are now available, for example, terfenadine, astemizole and loratadine (Bradley & Nicholson 1987; Nicholson 1982; Nicholson & Stone 1982), and are free of central effects.

#### INTERPRETATION

When the presence or absence of impaired performance has been established the findings need careful interpretation. Impaired performance not only implies impairment of a particular skill, but also that the central nervous system has been modified. Other skills that are less obvious and less easily measured may also be impaired. In this context, it is timely for the clinical pharmacologist to review with the psychologist the current approach to the measurement of behaviour and performance, and to ensure that current knowledge is being taken into consideration. Inability to show impaired performance does not necessarily mean a drug is free of adverse effects, as there is no test or group of tests that show whether human performance *in toto* is preserved.

It must also be appreciated that the data on impaired performance with drugs may be obtained in young healthy adults. Further, the effects of centrally acting drugs may vary with age and gender and the ability of the individual to metabolize and excrete the drug, and effects may be enhanced by the concomitant use of other drugs. Impairment of the ability to metabolize a drug as in those with renal failure must also be taken into consideration. There

is also clear evidence that the elderly are more sensitive to psycho-active drugs, and the effects of drugs may vary from young adulthood to middle age.

There are no simple answers to the questions that are raised by performance studies with drugs. We must be wary of studies which claim absence of performance deficits, and interpret with caution studies that claim to show impairments. It is important that sensitive techniques are used. Ideally, a drug in which impaired performance of any nature cannot be demonstrated in an adequately designed experiment is required. However, other things being equal, limited impairment of performance may have to be accepted, and the drug that is least likely to impair performance may have to be chosen.

#### GENERAL CONSIDERATIONS

Though rapidly eliminated hypnotics and antihistamines free of central effects are now used widely by those involved in skilled activity, problems remain with many other drugs. Particular difficulties arise with psychoactive drugs, such as antidepressants and anxiolytics, which are used for their daytime effects. Of course, in patients with disorders of mood, treatment itself may lead to an improvement in performance, but the possibility of impairment with these drugs most certainly arises if they have sedative effects. The emergence of antidepressants free of sedation has been helpful, and some of the newer anxiolytics may have less sedative effects than others.

There is, however, increasing concern that some drugs without obvious central effects, such as the beta-adrenoceptor antagonists, may have central effects of a subtle nature (Currie *et al.* 1988; Nicholson *et al.* 1988). In this context disturbance of memory should be borne in mind. The safe use of these drugs may well rest with compounds that cross the blood-brain barrier with difficulty, though the question also arises whether tolerance to drugs of this group, even if they cross the blood-brain barrier very slowly, develops in the same way as it would appear to do so with other centrally active drugs. Much more needs to be known about drugs now being used in the management of hypertension, and care may have to be taken in their use.

Most certainly a cautious approach to the use of drugs is essential in the proper management of those who are engaged in occupations where impaired performance would not be acceptable. The possibility that the individual may respond adversely with any drug must always be excluded, even for those drugs free of any experimental evidence of a central effect. Nevertheless, treatment has often to be decided on the basis of that which is least likely to cause harm, and it is fortunate that there are often many drugs available which, though they may have similar therapeutic efficacy, have different effects on performance.

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