SCREENING PROCEDURES IN VOLUNTEERS AND PATIENTS

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The chief object of screening procedures for psychotropic drugs is to get the maximum amount of information from the most economical series of investigations. The sheer volume of potential psychotropic agents requiring investigation each year makes it imperative to have quick, safe and effective screening methods before marketing new drugs commercially. Animal studies are of value as a first stage in screening, but of course they are no substitute for human pharmacological studies.

The position of the clinical psychopharmacologist investigating a new agent is similar to that of a fisherman in an imperfectly charted sea. Preliminary studies have indicated where he should fish but he has to decide which diameter of mesh he uses in his net and at what depth he fishes. He can err either by catching so many different kinds of fish he is unable to sort out those he particularly wants, or he may use so wide a mesh or fish at the wrong depth so that he catches none at all. The clinical psychopharmacologist needs to have some principles in investigation so that such errors are kept to a minimum.

There are some guidelines in evaluating psychotropic drugs but they can hardly be described as principles in the present state of our knowledge. Many of them are empirically rather than scientifically based and perhaps it is right that this should be so. The psychopharmacologist must always remind himself when he is investigating a new drug that behind him is a host of clinical psychiatrists asking the same questions about each new agent: Is it safe? Which type of patient should it be prescribed for? By what route should the drug be administered? How often should the drug be taken, in what dose and for how long? What are the unwanted effects of the drug?

I shall deal with each of these separately and illustrate the value of screening by describing some personal work with some drugs which are not normally considered to be psychotropic agents, the β -adrenoceptor blocking drugs, propranolol and sotalol. The latter is a new drug at present being investigated in Britain before market submission and the former has been a well established agent in general medicine, particularly in cardiology, since 1964.

Safety

Although this subject is very important the problems it poses are not specific to psychopharmacology. The stringent precautions imposed by the Federal Food

and Drug Administration (FDA) in the United States and by the Committee on Safety of Medicines in the UK ensure that most new drugs are safe by the time they are approved for testing in man. Nevertheless it is imperative that, during the screening of a new agent, tests of haematological, renal, hepatic and metabolic functions are carried out after short-term and long-term administration of the drug. Whether or not these tests should be carried out in volunteers or patients is debatable. There is scientific merit in choosing patients rather than volunteers (Oates, 1972) and I believe the ethical objections to using volunteers (including prison 'volunteers') in long-term studies are so overwhelming that such toxicological investigations cannot be justified.

Frequently the dangers of drugs are first noticed by careful clinical observation; the discovery of the 'cheese reaction' with monoamine oxidase inhibitors (Blackwell, 1963; Samuel & Blackwell, 1968) is a good example of this. As screening of a new drug includes its first administration in man the investigator must be constantly on the watch for any untoward effects. Unpredicted or bizarre symptoms must be taken seriously, even in those psychiatric patients whose complaints appear to be unrelated to medication.

Unfortunately we are not yet able to screen those psychotherapeutic drugs which are prone to abuse. If a drug shows rapid development of tolerance it should be viewed with suspicion. Tolerance is better detected using some dose schedules than others (see below). The presence of physical withdrawal symptoms after stopping the drug is also an indicator of potential abuse (Hollister, 1962). For this reason it is often helpful to continue clinical assessments for some days after ceasing treatment. Oswald, Lewis, Dunleavy, Brezinova & Briggs (1971) have recently shown the value of this in assessing the possible dangers of fenfluramine and imipramine.

Clinical indications

In many instances there is sufficient evidence from animal experiments to indicate to the clinical investigator which are the likely therapeutic effects in man. However, the history of psychopharmacology makes it abundantly clear that major advances are likely to be made through observation of drug effects in human rather than animal subjects. Our screening must therefore be flexible and versatile.

The first phase of screening should be in volunteers. This viewpoint is now generally accepted; in a recent postal enquiry of academic and industrial clinicians engaged in drug research, 90% felt that volunteers should be the first population studied in the clinical evaluation of a new drug (Blackwell, 1972). This being said, it is important to emphasize that this order of procedure is not primarily determined by the clinical indications for the drug. Hollister (1972) has reviewed the value of volunteer studies in predicting the therapeutic use of psychotropic drugs. Although sedative and stimulant drugs have actions in normal man which correctly predict their effect in patients, this is not true of antidepressive or antipsychotic drugs. For example sedative effects were found with meprobamate in normal subjects which correlate with clinical use (Hollister, 1962) but very similar effects were found with chlorpromazine and thioridazine in volunteers (Hollister, Kanter & Wright, 1968) and there was no evidence of any effect which might be useful in the treatment of schizophrenia or hypomania. Our chief problem is that we have no experimental equivalents of schizophrenia and other psychoses which can be reproduced in the laboratory.

We are therefore compelled to use the clinical trial as our main indicator of therapeutic benefit in these disorders. It is out of place here to discuss the principles of clinical trials but I should like to point out that as a screening procedure it is preferable to have a small homogeneous sample of patients rather than a large heterogeneous one. For example, in the evaluation of a new antidepressive drug it could lead to misleading results to test it initially in a general practice population. Benefit might be noticed but in this population a sedative effect alone may bring clinical relief (Wheatley, 1972). If a homogeneous sample is chosen misconceptions such as the labelling of monoamine oxidase inhibitors as antidepressive drugs on inadequate evidence (Tyler, 1973) can be prevented. Our diligent investigator may only spend a few months in his screening of a new drug but his conclusions may shape prescribing habits for a generation.

Route of administration

This is usually not determined by the clinical investigator but by the pharmaceutical manufacturer in the preparation of his product. It is nevertheless important to emphasize that results obtained through investigations of the drug's actions using one route of administration may not apply if the drug is given by a different route.

Frequency and dose of administration

Dose schedules are an important part of any screening programme and in the past too little attention has been

paid to them in the evaluation of psychotherapeutic agents. The best schedule can be determined from knowledge of both the pharmacokinetics of the drug and its pharmacological and clinical response. In the evaluation of sedative agents it is dose which determines whether the drug is an anti-anxiety or a hypnotic agent, and we must not allow ourselves to be beguiled by the pharmaceutical industry into thinking that there are qualitative differences between such drugs. Volunteer subjects are ideal in the early investigation of dose schedules. Single dose studies of sedative agents can define the likely hypnotic and anti-anxiety doses and the duration of their clinical effects are a guide to frequency of administration. Additional information of the metabolism of the drug (for example, knowledge that it has an active metabolite with a long half-life) may be extremely valuable in this regard. Other objective measurements such as the electroencephalogram, averaged evoked response and tests of cognitive and motor performance may be useful in establishing length of drug action and have proved particularly helpful in studying the hangover effects of hypnotics (Malpas *et al.*, 1970; Bond & Lader, 1972; Bond & Lader, 1973). Such measurements may give valuable information to the clinician but they must be correlated with subjective response if they are to be put to practical use.

Many other drugs, including antidepressive and antipsychotic agents, are different in that, although unwanted effects may occur immediately, therapeutic benefit is delayed. The investigator can only determine this in patients and clinical assessment must be carried out frequently so that the timing of response can be determined. This is a part of screening and is highly relevant to clinical practice. Studies in volunteers and patients can be synthesized to produce a drug administration schedule which is otherwise only achieved after years of trial and error in the clinic.

Dimascio & Shader (1971) have shown how irrational are the dose schedules of many of the psychotropic drugs in current use and I am sure that inadequate screening is in large measure responsible for this. The ritual of a three or four times daily dosage tends to be slavishly followed when the drug is first prescribed, and even though later clinical and pharmacokinetic evidence shows this to be unnecessary the schedule persists. Phenothiazines and tricyclic antidepressants seldom need to be prescribed more than twice daily and once patients are stabilized on the drugs intermittent withdrawal for 1–2 days at a time carries no danger of relapse.

In deciding on the most effective dose of a drug a range of different doses has to be tested. In the treatment of psychoses a series of fixed dose schedules is necessary but in those neurotic disturbances such as excessive anxiety, in which relief of symptoms occurs soon after drug administration, flexible dose schedules are more appropriate. The patient chooses the dose that affords most clinical relief with a minimum of

Unwanted effects

significant, and the least easy to detect. Measurement of unwanted mental effects may be correlated with pharmacokinetic ones and the combined information can play an important part in deciding the dose schedule. Thus a tricyclic antidepressive drug such as amitriptyline, which has immediate sedative and autonomic side-effects but delayed therapeutic ones, may be administered at night in a single dose, not only to facilitate sleep but also to reduce discomfort caused by autonomic effects to a minimum.

The screening procedures for each type of psychotropic drug are summarized in Table 1. The investigator usually has indications of the type of agent he is testing from animal studies and this should be sufficient to choose which screening procedure is most appropriate. It cannot be emphasized too strongly that this should be viewed as a guide rather

Table 1

Figures 1 and 2 Effects of racemic propranolol (▲—▲) and dextropropranolol (■—■) on subjective anxiety (Figure 1) and pulse rate (Figure 2). ○—○, placebo; ●—●, diazepam. The scores are given as differences between first and second occasions of testing. Any pair of means further apart than the critical difference (CD) are significant at the 5% level.

than a rigid procedure. The limitations of current screening methods are shown by the complete absence of procedures for the evaluation of a novel agent such as lithium in the prophylaxis of recurrent affective illness. There is no alternative to trial and error evaluation in patients for such types of agent.

Screening of β -adrenoceptor blocking drugs in psychiatry

Although β -adrenoceptor blocking drugs are relatively new to psychiatry they have been studied intensively in medicine. Thus in screening their potential use in psychiatry we had the unusual advantage of a fund of detailed information on the pharmacokinetics and pharmacological effects of one of the drugs, propranolol, in human subjects. In particular it was known to be a very safe drug in healthy subjects (Stephen, 1966). Perhaps it is too much to expect so much initial pharmacological data with most psychotherapeutic drugs but it may be an augury for the future.

Because previous work suggested that propranolol was effective in the treatment of anxiety (Granville-Grossman & Turner, 1966; Wheatley, 1969) our first task was to establish whether the drug had sedative effects. Propranolol was compared with a new β -adrenoceptor blocking drug, sotalol, and placebo. As sedative effects were being considered it was appropriate to use volunteer subjects in the first instance. Six subjects took a single dose of 120 mg racemic propranolol, 240 mg racemic sotalol and placebo on three separate occasions. Order effects were allowed for by using a Latin square experimental design. After each drug, effects were recorded after 1

and 3 h; these included the central physiological measures of the electroencephalogram, and mean auditory evoked response in addition to peripheral measures and ratings of subjective mood and bodily feelings. The results showed that even with the comparatively large doses used in the experiment that there were no unequivocal central sedative effects (Lader & Tyrer, 1972).

Sotalol produced mood changes which could have been the first signs of sedation but propranolol had no such effects. Significant β -adrenergic blockade (as measured by fall in pulse rate) was present at 1 and 3 h but degree of β -blockade did not correlate with plasma levels of propranolol. As it is known that propranolol after oral administration is metabolized to an active metabolite, 4-hydroxypropranolol (Coltart & Shand, 1970), this absence of relationship was not unexpected.

The next stage in screening was a matter of choice. The drugs could be given in higher dosage to see if important central effects were present, or they could be given in lower dosage. In effect, the choice was made by a homogeneous sample of chronically anxious patients who took sotalol and placebo for 2 weeks each in a trial of sequential design. A flexible dosage regimen (80–800 mg/day) was allowed. The results showed that sotalol was of some benefit in these patients and that this was achieved on a mean dose of only 124 mg/day (Tyrer & Lader, 1973). The patients had given the answer to our question. The question of central effects in higher dosage thus seemed to be irrelevant in the relief of neurotic anxiety, although it may be important in other conditions (Atsmon, *et al.*, 1971; Steiner *et al.*, 1973).

Once a lower dosage range had been chosen the

Figure 3 Differential response to racemic propranolol in somatic (O--O) and psychic (●--●) anxiety. (CD=critical difference).

next step was to establish whether clinical benefit was due to β -adrenergic blockade or to other actions. Racemic propranolol was therefore compared with its dextroisomer, which has only 1/60 of the β -blocking activity of the racemic mixture (Howe & Shanks, 1966), diazepam (a centrally acting sedative) and placebo in an experiment in which drug effects were measured in induced anxiety. Paid volunteer subjects ran the gauntlet of a series of unpleasant stresses designed to produce anxiety; these included electric

shocks to the arm before and after the administration of isoprenaline and exposure to specially selected phobic stimuli such as snakes, rats and spiders. Physiological and subjective measurements were recorded during these stresses before and after drug administration. The results showed that only diazepam significantly relieved anxiety and that racemic propranolol was marginally less effective than dexpropranolol (Figure 1) despite producing greater β -blockade (Figure 2) (Tyrer & Lader, 1947b).

Thus a direct relationship between relief of anxiety and degree of β -blockade could be ruled out. Possible reasons for the results came from a simultaneous study carried out in anxious patients in which racemic propranolol was compared with diazepam and placebo. On this occasion patients were selected so that they comprised two groups, one which emphasized the somatic symptoms of anxiety and the second which emphasized the psychological aspects of their condition. The results showed that patients with psychic anxiety fared significantly worse on propranolol than did patients with somatic anxiety (Figure 3) (Tyrer & Lader, 1974a). If induced anxiety is considered as a form of psychic anxiety the results of the previous study fall into perspective.

These studies were carried out between 1971 and 1973 and involved 38 volunteers and 31 patients. One definition of screening had been achieved in that the number of individuals testing the drugs was small. Whether the results were adequate to satisfy the second definition, that of illuminating the clinicians, is for them and posterity to decide.

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