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EDITORIAL

Drug assays in neuropsychiatry[1]

INTRODUCTION AND GENERAL PRINCIPLES

The measurement and interpretation of plasma concentrations of drugs are beset by numerous problems and, up to the present time, these have militated against their routine use in neuropsychiatry. In other areas of medicine, however, drug assays have proved to be of clinical importance, and experience here has allowed the establishment of a number of principles.

Measurements of plasma steady state concentrations of anticonvulsants, for example, have led to their use in the following areas: in establishing non-compliance (especially with out-patients); for detecting abnormalities of absorption; in the differentiation of some toxic signs from those of primary brain disorder; in evaluating excessive metabolism due to liver microsomal enzyme induction from previous or concurrent treatment with other drugs, especially in non-responders; and, finally, in the evaluation of patients suspected of complex drug interactions. Measurement of plasma non-steady state concentration following single dosage has occasionally been mooted as being of predictive value in relation to therapeutic response.

Unfortunately, the situation is less clear with respect to drugs currently used in neuropsychiatry for a number of reasons.

First, less precise information is available concerning the pharmacokinetics in man, due to the high volume of distribution of lipophylic drugs and in many instances the very high degree of plasma protein binding.

Secondly, the existence of numerous metabolites, the concentrations of which vary widely and some of which are pharmacologically active, leads to a poor correlation between drug pharmacokinetics and pharmacodynamics. To this may be added the fact that many drugs used in neuropsychiatry are rapidly absorbed, leading to wide fluctuations in plasma levels, which in itself leads to difficulties in interpretation.

Thirdly, a problem exists in the laboratory concerned with the accurate measurement of the very low levels of drugs encountered and the associated metabolites.

Finally, considerable difficulties arise over precise clinical evaluation of response in patients with medium- to long-term disorders, the natural history of which is characterized by a fluctuating course and in which even precise diagnosis of a homologous group of disorders is frequently difficult.

It is perhaps not surprising, therefore, that it has proved difficult to establish therapeutic ranges; moreover, different ranges will be applicable, dependent upon whether one is interested in the management of the acute phase of illness, prophylaxis against relapse, or the identification of specific features of toxicity. By analogy with other groups of drugs, considerable individual variation, possibly genetically determined, is likely to be encountered, and different therapeutic ranges (as well as dosage) will be required for children and for the elderly. Factors such as diet and fasting which are associated with varying levels of free fatty acids in plasma will affect protein binding of drugs and where this is high, as is frequently the case with drugs used in neuropsychiatry, only small changes in binding will have large effects on the free fraction. Both pregnancy and disease states associated with alterations in plasma proteins give rise to similar problems.

Unfortunately, measurement of the free fraction of any drugs in plasma is not practicable on a routine basis at the present time for technical reasons, although trials of commercial kits are currently in progress in the United States. Estimations in saliva are also rather unsatisfactory for practical reasons and cerebrospinal fluid (c.s.f.), although ideal in many respects, is, of course, not available.

Even when these problems have been overcome, it will be appreciated that the use of serial steady

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state plasma levels of drugs is only one additional factor to be taken into account in the overall clinical management of the patient and that no account is taken in these measurements of any variations due to passage through the blood–brain barrier or of the tolerance at receptor level based on drug-induced changes of endogenous modulators.

Alternative approaches (as, for example, by analogy with measurement of prothrombin time as a monitor of anticoagulant therapy) have been suggested and, in neuropsychiatry, this has usually involved measurement of serum prolactin response to dopamine blockers or platelet monoamine oxidase (MAO) activity as a monitor of the activity of MAO inhibitors; these parameters will be considered later.

Against this background must also be set the great cost of monitoring drug therapy. Nevertheless, recent developments in both the clinical evaluation of patients and in laboratory techniques – in particular the routine application of a high performance liquid chromatography (HPLC) and radioreceptor binding – point to possible changes in the situation in the near future and warrant an evaluation at this time of the position with respect to individual groups of drugs currently used in neuropsychiatry. In this review, hypnotics and drugs used in the treatment of premenstrual tension have not been included, and no account has been given of tests for drugs of abuse, although routine rapid semiquantitative tests for a range of these by homologous enzyme immunoassay, using the EMIT (Syva) techniques, are now available.

NEUROLEPTICS

These will be considered under three headings: the phenothiazines, the thioxanthenes as illustrated by flupenthixol, and the butyrophenones as represented by haloperidol.

The phenothiazines

A vast literature exists on the measurement of blood levels of this group of drugs and the relationship of these to clinical effects. While there is some evidence that low plasma concentrations are found more frequently in non-responsive schizophrenics (Smith *et al.* 1979), and it is reported that concurrent lithium therapy may lower plasma chlorpromazine levels (Rivera-Calimlin *et al.* 1978), the value of monitoring in individual patients is very limited. As a group these drugs are lipophylic, having a large volume of distribution, and are highly bound to protein (Freedberg *et al.* 1979). Many metabolites exist, the concentrations and pharmacological activity of which vary considerably, and the absolute plasma concentrations are frequently low, being near to the limits of detection by conventional laboratory methods. Variable bio-availability as a result of hepatic metabolism and enzyme induction, and degradation within the gut wall are further complications (Dahl & Strandjord, 1977; Bergling *et al.* 1975; Smith *et al.* 1979). For details of particular drugs, the reader is referred to review articles (Cooper, 1978; May & Van Putten, 1978).

Two papers, however, warrant special attention. Creese & Snyder (1977) described a simple, sensitive radioreceptor assay (RRA) for anti-schizophrenic drugs in blood; and Tune *et al.* (1980) applied this to correlate serum neuroleptic levels with clinical state, monitored by an abbreviated version of the Present State Examination (mini-PSE). They found a significant correlation between serum neuroleptic levels and clinical response, but not between drug dosage and blood levels, or between dosage and clinical response. They argue that the failure of some reports to correlate drug levels with clinical response may be (*a*) due to the system of patient evaluation; and (*b*) because the non-receptor binding techniques might not have taken account of the activity of pharmacologically active metabolites.

Flupenthixol

Johnstone *et al.* (1980) estimated plasma levels of flupenthixol by radioimmunoassay (RIA) and RRA in acute and chronic schizophrenic patients. Both isomers were detected in blood after administration orally and by depot injection but, although a good clinical response and raised serum prolactin

levels were associated with the administration of α-flupenthixol, no correlations between these and plasma levels of the drug were found. Some reduction in platelet MAO activity was also detected, but this too was unrelated directly to plasma flupenthixol levels. Concurrent administration of the anticholinergic drug, procyclidine, reduced plasma levels of flupenthixol, even when given parenterally. Trimble (personal communication), using α-flupenthixol as an antidepressant in much lower doses, also measured plasma levels and found that, although there was no direct correlation between plasma levels of the drug and improved clinical states, there was a positive correlation between drug levels and serum prolactin one month after commencing treatment and between serum prolactin and clinical improvement at two months.

Haloperidol

No convincing evidence exists for the value of measuring plasma concentrations of haloperidol as a guide to clinical response with acute or chronic disorders of any age-group, although correlates do exist between side-effects and plasma levels, especially in children (Morselli & Zarifian, 1980). According to one report, however, correlation does exist between dose and plasma levels and between plasma levels and serum prolactin, especially in higher dose regimes (Evans *et al.* 1978).

There is no evidence that in non-responders there is a lack of bio-availability of the drug (Morselli & Zarifian, 1980).

DRUGS USED IN THE TREATMENT OF DISORDERS OF MOOD

Tricyclic antidepressants

Detailed studies on the pharmacodynamics of this important group of drugs have been made since their introduction in the late 1950s. There are few differences in clinical response within the group as a whole, although amitriptyline is rather more sedative than the others. All are rapidly and completely absorbed from the gut and plasma steady states are readily achieved. Inter-patient variations occur, however, with respect to the rate of liver detoxication, possibly on a genetic basis, and are also dependent upon age, elderly patients being slow detoxicators (Nies *et al.* 1977). Demethylation converts imipramine to desimipramine and amitriptyline to nortriptyline, both of which are pharmacologically active products.

Burrows (1977) and Braithwaite (1980) have reviewed the literature with respect to the relationship between clinical response and plasma levels for individual tricyclics. Although there are some conflicting reports, there appears to be considerable evidence for the existence of a curvilinear relationship between plasma levels and clinical response, the exact reasons for which are not clear. It is certainly not simply due to the fact that non-responders are prescribed larger doses of drugs, but rather it would appear that higher levels of these drugs inhibit their own pharmacological action.

In those trials where a lack of correlation between plasma levels of tricyclic antidepressants and clinical response has been reported, possible explanations lie in the difficulties inherent in the measurement of clinical response, heterogeneity of group diagnosis, and the effects of other concurrent drug administration (Braithwaite, 1980). The relationship of blood levels to neuropsychiatric side-effects, however, is less clear. It is established that a good relationship exists between dose and plasma levels and between plasma levels and cardiotoxicity; the latter factor alone may be crucial in excluding regimes employing higher levels, especially in elderly patients (Burrows, 1977). Interactions between barbiturates and tricyclics and between neuroleptics and tricyclics which result in altered blood levels have been described; again, implications for the elderly are important (Burrows, 1977).

Most authorities would probably agree that plasma monitoring of levels of these drugs does have a place in the detection of non-compliance, the management of non-responders, and as a protection against cardiotoxicity.

It is important also to note that the tricyclic antidepressants have epileptogenic properties (Trimble, 1978; Nawişhy *et al.* 1980) and that, if anticonvulsants are administered concurrently, these will interact and reduce plasma levels of the tricyclics (Richens, 1976).

Maprotiline differs structurally from conventional tricyclic antidepressants only by the introduction of an ethylene bridge into the molecule, a change which is probably not sufficient to warrant its classification as a separate class of psychotropic agent. Clinical differences do exist, however, but the evidence for correlation between plasma levels and clinical response is not clear and has been reviewed by Burrows (1977) and Pinder *et al.* (1977).

TETRACYCLIC ANTIDEPRESSANTS

Coppen *et al.* (1976) found that plasma levels of mianserin were constant for individual patients on a standard dose, although the highest concentration was some four times the lowest in different patients. No correlation was demonstrated between plasma levels and either therapeutic response or side-effects. By contrast, Perry *et al.* (1978) did find a correlation between plasma concentration and changes in the Hamilton Rating Scale for depression.

In the largest study by Montgomery *et al.* (1978), a curvilinear relationship in plasma levels was correlated with optimum therapeutic response and a significant clinical disadvantage established with high plasma levels, particularly in endogenous depression and in patients over the age of 55 years.

Nomifensine

Nomifensine is a relatively new drug introduced for the treatment of depression. It is a non-tricyclic, non-MAO inhibitor compound which inhibits presynaptic noradrenaline re-uptake but, in addition, has dopamine agonist properties (Costall & Naylor, 1977; Brogden *et al.* 1979). Few studies have been carried out as yet on the value of monitoring plasma levels in relation to direct response but it would appear that, after the establishment of steady state kinetics, low levels are associated with sub-optimal clinical response (Nawishy *et al.* 1980). However, on the basis of acute dosage it would appear that there is a dissociation between pharmacokinetic and pharmacodynamic responses, implying either the formation of an active metabolite, or access to a deep compartment receptor, or both (Saletu & Taeuber, 1980). This is confirmed by the efficacy of once daily dosage, in spite of a half-life of 2 hours (Hanks *et al.* 1980).

Further studies of larger series are awaited but, for the present, there is no indication for routine monitoring of plasma levels.

Monoamine oxidase inhibitors

Methods exist for the direct measurement of MAO inhibitor drugs in plasma but, in practice, these are seldom used, attention being directed more towards measuring the degree of inhibition of the enzyme monoamine oxidase itself, especially in platelets (Robinson *et al.* 1978). Technical problems exist, however, in that baseline levels vary widely and different results are obtained with the use of different substrates.

Some correlation, however, does exist between high degrees of enzyme inhibition and clinical response, although there is a marked dissociation in the early stages of treatment (Robinson *et al.* 1978), suggesting that the pharmacological effect of these drugs may not be confined to this mechanism alone.

Lithium

Lithium salts have been used in the UK since 1949 but only since 1970 in the USA. They are administered for both the management and prophylaxis of manic-depressive disorders (Srinivasan & Hullin, 1980; Baldessarini, 1980). Rapid and complete absorption results in wide fluctuations in plasma levels (Crammer *et al.* 1980). Considerable variation occurs between patients but, for a given individual, the pharmacokinetics appear to be relatively constant.

The distribution of lithium in the body is wide, gradients across membranes being small (unlike sodium and potassium) and plasma protein binding is minimal. Nevertheless, penetration of the blood–brain barrier is poor and c.s.f. concentrations are only some 40 % of plasma values.

Plasma levels should be monitored regularly to assess compliance and also, in particular, as a precaution against toxicity. In this connection it is worth emphasizing the special situation of renal conservation of lithium in states of sodium depletion.

There is a lack of precise information concerning the therapeutic ranges required for the management of acute manic-depressive disorders and for prophylaxis, although it is likely that higher levels will be necessary for the former (Baldessarini, 1980).

Anxiolytics as exemplified by the benzodiazepines

Most investigators have reported a poor or absent correlation between plasma levels of benzodiazepines and clinical effect (Bellantuono *et al.* 1980; Bond *et al.* 1977), although correlations do exist between plasma levels and dose (Rutherford *et al.* 1978). Reasons for poor correlations include: difficulties in the assessment of clinical response, including those related to drug tolerance which is a particular feature of benzodiazepine therapy, and the inability to date of laboratory techniques to measure metabolites accurately. A further difficulty arises as a result of the very different pharmacokinetics of the various benzodiazepines (Bellantuono *et al.* 1980; Shader & Greenblatt, 1980).

In two surveys, however, a correlation between plasma levels and clinical response has been stressed (Curry, 1974; Dasberg *et al.* 1974); others have claimed a more limited use in relation to compliance, abuse and intoxication (Shader & Greenblatt, 1980).

Recently, an investigation has shown a good correlation between one highly specific clinical parameter capable of exact measurement by peak velocity of saccadic eye movements and serum benzodiazepine concentration in acute single dose experiments in man (Bittencourt *et al.* 1981), but the implications for this finding in the wider clinical context must remain speculative for the present. It is to be hoped, however, that this most interesting observation will pave the way for similar studies in the future.

In this connection, too, the recent development of reliable HPLC methods for the measurement of individual benzodiazepines and their metabolites (Peat *et al.* 1979) is clearly important; but perhaps of even greater significance is the development of radioreceptor binding assays for this group of drugs which are capable of measuring the total free benzodiazepine binding of pharmacologically active moieties at specific brain receptors on a regional basis, dependent upon preparation of membranes from animal tissue.

CONCLUSION

There is, at the present time, considerable interest in the monitoring of plasma levels of drugs used in neuropsychiatry and, as laboratory techniques become more sensitive and specific in the future, this is likely to increase. The range of drugs now available is too large to allow general conclusions to be drawn and each group requires to be evaluated on its own merits.

The indications for monitoring plasma levels of neuroleptics and benzodiazepines are limited at the present time but these are currently areas of intense research.

Therapeutic ranges are quoted for the antidepressants but larger trials will be needed to establish unequivocally the place for monitoring in routine patient management.

Regular measurements of lithium concentrations in plasma are essential as a precaution against toxicity.

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