Drug Treatment of Epilepsy

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Foreword by Dieter Janz
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Foreword

The treatment of epilepsy has always been of two types: dietary and pharmacological. However, while dietary management—understood in the older, fuller, sense—has always remained essentially the same, drug therapy has changed continually.

Developments in drug treatment over the years and the introduction of new antiepileptic drugs have often been noted: bromides in 1857, barbiturates in 1912, hydantoins in 1938, oxazolidinediones in 1946, succinimides in 1951 and benzodiazepines in 1966. The most recent development in the drug therapy of epilepsy is not, however, characterized by the introduction of new drugs but by the development of a new clinical discipline—pharmacokinetics.

Whether because new drugs have become so numerous, or because demands for proof of efficacy and safety have increased, it is now necessary to know whether a drug is absorbed quickly or slowly, in part or completely, into which substances and by which pathways it is metabolized, what properties its metabolites have, and how both the parent drug and its metabolites are distributed and eliminated.

This study has led not only to an understanding of the mode of action of new drugs but also to a better understanding of the few well-established antiepileptic drugs. With the introduction of laboratory techniques for the qualitative and quantitative determination of antiepileptic drugs in body fluids, questions which hitherto could only be tested empirically can now be answered rationally: questions, perhaps, about the presence of a therapeutic or a toxic blood level, about the dosage form, its absorption and distribution, and about interactions with other drugs, with illnesses or stress situations which might increase or decrease the drug's effect.

The emergence of the discipline, pharmacokinetics, also created the need for a monograph; one which, because of the importance to clinical practice of the subject, could be written only by a clinically qualified pharmacologist. Alan Richens, moving to and fro between laboratory and hospital ward, has made fundamental contributions to the

pharmacokinetics of antiepileptic drugs. From his own knowledge and experience he is familiar with both the laboratory techniques of the pharmacologist and with the clinical skills of the physician. There is, then, a guarantee that this monograph will serve both the advancement of knowledge and the well-being of the patient.

October 1975

DIETER JANZ
Professor of Neurology
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Preface

In this monograph I have reviewed three aspects of antiepileptic drug therapy: clinical pharmacology, evidence of efficacy, and adverse effects and interactions. Where possible I have considered only those studies which have been adequately controlled – in some areas this has left little to write about. Although most of the currently used drugs for treating epilepsy have been in use for at least ten years, phenobarbitone for over sixty years, remarkably little scientifically acceptable evidence of efficacy is available. For this reason rational prescribing in some types of epilepsy is not possible, a fact which becomes striking when one realizes how diverse and contradictory are the opinions expressed in 'authoritative' textbooks. Because of this deficiency, a final chapter outlining the requirements of a controlled clinical trial of an anti-epileptic drug has been added as a guide to those who wish to perform a well-designed clinical trial rather than another uncontrolled study of the 'case-report' type.

I would like to thank Dr John Laidlaw for stimulating my interest in the drug therapy of epilepsy and for his encouragement in performing most of the personal research which is cited in this monograph. I would also like to thank Dr Geoffrey Houghton for collaborating with me in these studies, and the British Epilepsy Association for their financial support. Finally, I thank Miss Hazel Boughton for her patient secretarial assistance in preparing the manuscript, and the Medical Illustration Department at St Bartholomew's Hospital for preparing the illustrations.

October 1975 A. RICHENS

Introduction

For the great majority of epileptic patients long-term drug therapy represents the only practical form of treatment. Although neurosurgery can be highly effective, it is appropriate in only a small number of patients. Therefore, once a firm diagnosis of epilepsy has been made, the causative lesion, if there is one, identified, and the indications for neurosurgery excluded, the problem becomes largely a pharmacological one. Sometimes the social worker or psychiatrist will have to be involved because a disturbed family background, over-protection of or discrimination against the child with epilepsy may generate social and behavioural problems of some magnitude, particularly in a child already handicapped by some degree of brain damage either causing or consequent upon his fits.

Nevertheless, the problem common to all patients is that of fits and how to stop them. Pharmacological agents have become the standard form of treatment and are likely to remain so in the foreseeable future, and it is therefore important that they are used as skilfully as our present knowledge will allow. Although effective drugs have been used in epilepsy for many years, bromides since 1857, phenobarbitone since 1912 and phenytoin since 1938, only comparatively recently have we begun to learn something about the way they are handled in the body. Not surprisingly, this knowledge is having a considerable influence on the clinical usage of the drugs. This development has occurred because technological advances have provided sophisticated analytical equipment for measuring drugs at low concentration, and it is now possible to monitor most of the clinically-used anticonvulsant drugs in serum and other biological fluids. Because of the complex nature of methods of measuring drugs and of kinetic studies in man, a separate specialty, *clinical pharmacology,* has been created to collate information on the use of all types of drug in healthy and diseased man.

Whereas the clinical neurologist has used anticonvulsant drugs in an empirical fashion in the past, an approach which takes into account the kinetic behaviour of drugs can now achieve much better control of

epilepsy with a much smaller risk of toxicity. The most important fact to emerge from pharmacokinetic studies of these drugs is that a wide variation in serum levels can occur from one patient to another, even though each may be receiving the same dose of drug. Differences in absorption, distribution, and the rate of metabolism and excretion account for this variation, but for some drugs it is not possible to predict whether an individual will have a toxic or sub-therapeutic level on a given dose without actually administering the drug and measuring the level. Here, then, is the chief value of monitoring serum levels. If a patient has uncontrolled fits despite a higher than average dose of drug, it is reassuring to the clinician to know that the serum concentration is sub-therapeutic and that he can make a further increment in dose without running the risk of intoxicating his patient. However, regular monitoring of serum concentrations is an expensive and time consuming exercise, and before we can justify measuring each drug in every patient we need to consider carefully what advantages are likely to be gained from a knowledge of the serum level. The first two chapters of this monograph will examine the pharmacokinetic principles upon which a rational use of antiepileptic drugs is based, and will then discuss the merits and demerits of monitoring drug levels routinely in the epileptic patient.

Chapter 1

Basic Principles: kinetics of antiepileptic drugs

The development of techniques for measuring serum concentrations of antiepileptic drugs has been a major advance in the management of chronic epilepsy. In the light of these estimations the dose of a drug can be adjusted much more precisely to within the therapeutic range without having to resort to the traditional practice of adopting a dose level a little below that which has provoked symptoms of toxicity in the patient. But the interpretation and skilful use of these estimations requires a sound understanding of the factors which determine the kinetic behaviour of drugs in man. For instance, a rheumatoid arthritic patient with a low serum albumin level may show signs of phenytoin intoxication at much lower serum phenytoin concentrations than usual because the drug is highly bound to plasma proteins, particularly albumin, and it is the concentration of the unbound drug which determines the pharmacological action of the drug. The purpose of this chapter is to summarize the information which has been gained from controlled clinical pharmacological studies of antiepileptic drugs. Phenytoin has been studied in greatest depth and it serves conveniently as a model drug to illustrate the normal and pathological factors which can modify a drug's action.

Absorption of antiepileptic drugs

Phenytoin is relatively insoluble in aqueous media: saturation occurs at a concentration of around 100 μg/ml. The rate of absorption of the drug is limited by this insolubility, but it can be improved in one of two ways (Glazko and Chang, 1972). Microcrystalline preparations, in which the crystal size has been substantially reduced, present a much greater surface area for dissolution to take place. The same effect can be achieved by administering the sodium salt of phenytoin, which is

much more soluble. Although it reprecipitates in the stomach as phenytoin acid, the precipitate is finely divided and is absorbed as well as microcrystalline preparations (Dill *et al.* 1956).

All the British approved and proprietary preparations contain the sodium salt, with the exception of Epanutin Infatabs, Trinuride (a combination of phenytoin, phenobarbitone and pheneturide) and phenytoin suspension, BPC. Thus, differences in the amount of drug available for absorption, the so-called 'biological availability' of the drug, are unlikely to be of importance between preparations in common use in adult epileptic patients in Britain. Fig. 1 illustrates a

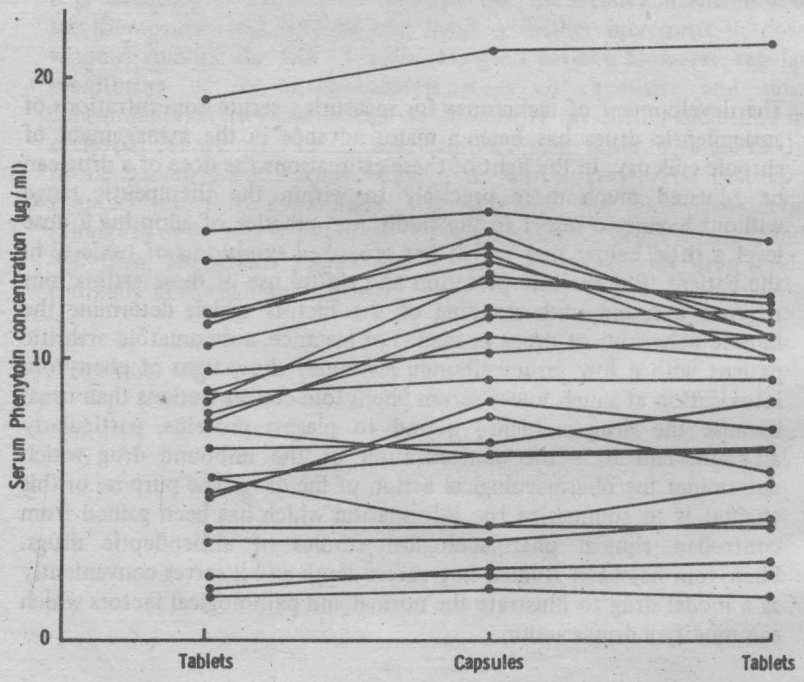

Fig. 1. Comparison of serum levels produced by phenytoin tablets (Boots) and capsules (Epanutin, Parke Davis). The serum phenytoin levels were measured in 24 patients who were stabilized on phenytoin tablets, and the estimations repeated 6 weeks after a change to the capsule preparation had been made, and again 6 weeks after a return to phenytoin tablets.

Mean phenytoin levels were: 8.0, 9.4 and 8.8 μg/ml respectively. (Hetherington and Richens, unpublished).

controlled comparison of phenytoin tablets and capsules. Although a slight increase in the mean serum concentration was found when a change was made to phenytoin capsules, the change was small and, furthermore, the concentration did not return to the previous value when tablets were substituted again, no doubt because the attention the patients received during the trial caused them to take their tablets more reliably. It can be concluded that if a real difference does exist between the two preparations it is small and of little clinical significance.

The same is *not* true in the United States and in Scandinavia where some preparations contain phenytoin acid and others contain the salt (Martin *et al.* 1968; Lund, 1974). Intoxication has occurred on changing from the former to the latter.

It is possible, although not formally studied, that in Britain children might be exposed to the risk of intoxication when Epanutin Infatabs, phenytoin suspension or phenytoin sodium capsules or tablets are interchanged. Only a small change in biological availability, perhaps 10% or less, can precipitate phenytoin intoxication because of the unusual kinetic behaviour of this drug. Phenytoin suspension BPC must be shaken thoroughly before use because precipitation of the drug will cause underdosing with the first doses taken from the bottle, and overdosing with the last doses. Intramuscular injection of phenytoin (as phenytoin injection BPC) is unsatisfactory because at the pH of the tissues crystals of phenytoin are formed which cause tissue damage and haemorrhage (Serrano and Wilder, 1974). These are poorly soluble and very slowly absorbed. Thus, changing to the intramuscular route for a few days (*e.g.* to cover an abdominal operation) may result in a fall in plasma concentration during injection, and a swing to toxic levels on resumption of oral therapy while absorption from the intramuscular sites continues (Dam and Olesen, 1966; Serrano *et al.* 1973; Wilensky and Lowden, 1973). A scheme for changing from oral to intramuscular phenytoin without causing a change in plasma concentration has been described by Wilder *et al.* (1974). They recommend giving an intramuscular dose 50% higher than the patient's oral maintenance dose in order to cover the medical or surgical emergency, and then on resumption of oral therapy half the original oral dose is administered for a period of time equal to the intramuscular period.

In order to make phenytoin sodium sufficiently soluble for injection, the manufacturers use a highly alkaline solvent, which is irritant to the tissues and can cause angiospasm on intravenous (or intra-arterial) injection. A ready-mixed parenteral preparation is now available which has a long shelf-life. Earlier preparations were unstable,

necessitating mixing the solvent and freeze-dried powder immediately before injection.

Unexpected problems with the biological availability of drugs can occur, as happened with phenytoin sodium capsules in Australia in 1968 (Tyrer *et al.* 1970). The manufacturers, in standardizing some of their preparations, changed the excipient (filler) from calcium sulphate to lactose. Doctors and pharmacists were not advised of this change because alteration of a supposedly inert substance in the capsules was not expected to influence the drug's absorption. Nevertheless, an outbreak of phenytoin intoxication ensued which was eventually traced back to this change in formulation. Presumably the calcium ions in the original capsules had reduced the biological availability of phenytoin, perhaps by formation of a chelate. It is interesting that there is some evidence that phenytoin reduces intestinal absorption of calcium (Chapter 9). Phenytoin capsules marketed in Britain contain a lactose excipient, not calcium sulphate.

Phenobarbitone is absorbed more rapidly than phenytoin, reaching a peak serum concentration 1-6 hours after oral or intramuscular administration (Jalling, 1974). Although preparations of phenobarbitone and its sodium salt are available, no compaiative studies of their absorption have been performed in man. Any difference which exists, however, is likely to be small. Methylphenobarbitone is twenty times less soluble than phenobarbitone and its absorption is therefore poor. As it is demethylated to phenobarbitone almost completely, there seems to be no good reason for its use in preference to phenobarbitone.

Like phenytoin, diazepam is poorly absorbed from intramuscular sites of injection. Peak serum levels are much higher, and occur much earlier, with oral administration (Hillestad *et al.* 1974). It should not, therefore, be used intramuscularly in status epilepticus; intravenous administration is essential (Chapter 7).

Comparatively little information is available on the absorption of the other antiepileptic drugs. With most, only one proprietary preparation is available in Britain, so biological availability problems with changes of brand do not occur. The prediction of a relatively rapid absorption for primidone was borne out in one study (Gallagher and Baumel, 1972b). Ethosuximide is rapidly absorbed, although peak serum concentrations occur later with capsules than with the syrup (Buchanan *et al.* 1969).

Distribution

After it has been absorbed, phenytoin binds reversibly to plasma proteins, mainly albumin. About 90% of the drug present in plasma is

bound. Removal of unbound drug, *e.g.* by metabolism, causes a reversal of binding so that the ratio of bound to unbound drug remains nearly constant. The concentration gradient which causes phenytoin to diffuse into the brain and other tissues is determined by the free drug in the plasma, not the total drug. Thus, the extent of binding is important in determining the clinical response and the development of toxic effects. Although there is, in general, quite good correlation between the serum concentration and signs of toxicity (Kutt, 1971), many exceptions are seen. One patient may show no sign of intoxication with a serum concentration that causes gross toxicity in another (Richens and Houghton, 1975). One possible explanation for this observation is that although the total serum concentrations in these patients are identical the concentration of free drug is much higher in the intoxicated patient. This has been examined by several workers, and although Booker and Darcey (1973) found a better correlation between clinical signs and the free rather than the total serum concentration, others have found that the degree of binding differs little between patients (Lunde *et al.* 1970). It seems unlikely, therefore, that differences in binding have more than a marginal influence on clinical response. It is probable that a difference in the neuronal sensitivity to the drug is a more important variable, but is, of course, more difficult to assess in a controlled manner.

As has been pointed out earlier, a reduction in the plasma albumin concentration will modify the clinical response to a given total serum phenytoin concentration because a smaller percentage of the drug is bound. The Boston Collaborative Drug Surveillance Program (1973) found this to be a highly important factor. Obviously, if an epileptic patient has a general medical condition which is likely to lower serum albumin it is essential to measure and allow for the abnormal protein level when interpreting a serum phenytoin result. Ideally, we should be measuring the concentration of free drug, but technically this is much more difficult than estimating total drug. The existing methods for separating free and bound drug are not entirely satisfactory and techniques in routine use for phenytoin do not provide adequate sensitivity for measuring free concentrations, which are, of course, only about ten per cent of the total. These difficulties explain the conflict between published reports on the binding of phenytoin (Eadie and Tyrer, 1974).

The cerebrospinal fluid (CSF) contains little protein compared with the plasma, and drugs which diffuse freely into it equilibrate with the concentration of unbound drug in the plasma. Thus, CSF can be regarded as an ultrafiltrate of plasma. This is convenient for the clinical