rational anti-epileptic drug therapy

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RATIONAL ANTI-EPILEPTIC DRUG THERAPY

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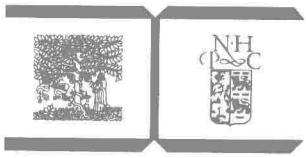

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RATIONAL ANTI-EPILEPTIC DRUG THERAPY

PREFACE

The development and growth of 'blood level determinations' has raised questions on the utility of the acquired data for the improvement of drug therapy. Most if not all epileptic patients require a certain amount of one or more body foreign compounds for their well or at least better being. It is recognized that choise of substance(s) and their amount has to be tailored individually in order to meet the very special demands of the patient in his particular condition.
By determination of these substances and their possible active metabolites the potencies are present to watch more carefully what amount may has actually reached the ' milieu interior' and the adequacy can be interpreted.
Not only the amount is important but also rate, extend and time-period at which the desired amount is maintained are indispensable in judging the course of treatment of patients.
The increased amount of information obtained from laboratory tests and observations relevant to treat and accompany the patient, requires a team management approach. The applicability of pharmacokinetics in this process has added a new expert to the already long 'cortege' at the bedside.

This book is meant to improve the communication between the patient and the physician and between the physician and those who traditionally in a delocated way directly are involved in the treatment of epileptic patients. An effort is made to use the acquired information, collected during the course of the clinical condition, for monitoring purposes for the patient himself. But from retrospective analysis this information can also be used in epidemiological studies on the efficacy of treatment of groups of patients. Also the influence of prescribed drugs on metabolic capacity of the other drugs in order to predict dosage regimens for new patients are included in this study.
It is hoped that this book may stimulate to extend these studies in two directions, one on larger populations allowing the descrimination of more variables, operating in the epilepsy-drug cycli and the second should focus on the pursuation of individual patients over longer periods of time in which the patient himselves actually participates in monitoring events.

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Peter van den Ham, neurologist, for critical evaluation of the manuscript, allowing us to present the complex material of pharmacokinetics more readily understood.

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CHAPTER 1.

INTRODUCTION

In our society one in every 200 persons suffers to a certain degree from epilepsy and is treated with anti-epileptic drugs.
(Lennox and Lennox 1960)
Although world wide figures are not available, it was indicated during the seventh international Symposium on Epilepsy (Janz 1976) that the general prevalence of epileptic disorders even might be higher.
The term 'Epilepsy' suggests that epilepsy is considered a disease, but due to complexity of the pathophysiological mechanisms which occur in different anatomical regions of the brain and appear as different electroencephalographic abnormalities, it should be considered as a group of disorders, ' the Epilepsies' (Sutherland et al 1974).
But in general Epilepsy is used as a synonym for the whole group of Epilepsies.

Clinically the seizures are the symptons of an episode of disturbed cerebral function, defined as epilepsy. Of course other types of disturbed cerebral physiology exist and have to be considered carefully by the physician before the diagnosis of epilepsy is stated. The general public remains very ignorant about epilepsy and tends to view the condition as a mental illness, therefore diagnosis poses problems for the patient as well as his relations and raises fear for the future. Also the aethiology of the seizure has to be considered as the seizure and may, besides brain pathology, be due to causes from outside the nervous system e.g. hyperglycaemia or uraemia. Overlooking the clinical and social problems with respect to epilepsy it will be difficult to give a definition of this disease.
The most complete one is presented by Sutherland and collegues (1974) who proposed *to define and regard epilepsy as a symptom of excessive temporary neuronal discharge due to intra cranical or extra cranical causes ; it is characterised clinically by discrete episodes, which tend to be recurrent, in which there is a disturbance of movement, sensation, behaviour, perception and/or consciousness.* It may be clear that such a complex disease results in a variety of types of seizures.

TABLE 1.

Most frequently used anti-epileptic drugs and their year of introduction.

Generic name	Trade name	Year of introduction
Phenobarbital	Luminal Gardenal	1912
Diphenylhydantoin Phenytoin	Dilantin Epanutin Diphantoin	1938
Primidone	Mysoline	1954
Ethosuximide	Zarontin Ethymal Emeside	1960
Diazepam	Valium	1963
Nitrazepam	Mogadon	1965
Carbamazepine	Tegretol	1969
2-Propylpentanoate Dipropylacetate	Depakine	1973
Clonazepam	Rivotril Clonopin	1975

These different types have been interpreted by the International Leaque against Epilepsy to propose a classification of epilepsy, based on seizure pattern translated in terms of probable site of origin in the brain with subsequent correlation of the primary criterion with aethiology (Gastaut 1969). This classification found wide acceptance by the clinicians and has played a part in a reduction of the confusion of terminology around the epileptic seizures.

For the treatment of this long feared disease, the modern physician has at his disposal about thirty drugs to which a more or less anti-epileptic efficacy has been attributed. A number of the most current compounds and their year of introduction is given in table 1.

Although some of the drugs are already in use over 50 years, little is known on the mechanism of action of the anti-epileptic drugs. In November 1977 a symposium, sponsored by the National Institute of Health (USA), was held with the aim to bring together authorities from the many scientific disciplines related to the subject who would explore the topics to be covered in a treatise on the fundamental aspects of anti-epileptic drug action. Although a lot of detailed research in animals takes place in the disparate disciplines resulting in current knowledge on cellular or regional level in the brain, it still is not possible to correlate these findings with the clinical efficacy of the anticonvulsants (Woodbury et al 1978)
The efficacy of these drugs have been subjected to a large number of clinical studies since their introduction. Their potency to reduce the number of seizures, without curing the origins of the desease, has been proven relatively well (Coatsworth, 1971, Mercier, 1973, Eady and Tyrer, 1974). Recently an extensive bibliography has been published, containing all available literature from 1900 - 1975 on Epilepsy (in two parts : Penry and Rapport, 1973 and Penry 1976).

In spite of the effort attempted, the anti-epileptic drugs are not able to bannish the seizures for all epileptic patients, actually even far from that. In 1968 Rodin described in a monograph about the future of the epilepsy the dissatisfaction of the physicians with the current medication. From his point of view one in every three patients treated was insufficiently 'seizure free'.

The obscurities about the exact indication of the various anti-epileptic drugs and the clinical and social problems which occur during chronic treatment of epileptic patients contributed to the fact that usually a combination of two or more drugs is prescribed by the attending physician. Also the point of view that epilepsy may be treated safer and more effective by individual adjustment of the daily dose of anti-epileptic drugs is generally accepted. However the benefit of plasma concentration measurements of these agents is not sufficiently appreciated (Eady and Tyrer 1974).

The possibilities to measure plasma concentrations of anti-epileptic drugs were rapidly recognized after their introduction. However it was not until the end of the sixties or early seventies that the determination of plasma concentrations to support the epilepsy treatment could be applied at a larger scale, mainly due to improvement of the analitical techniques (Penry et al 1972).
Nowadays plasma concentrations are performed in a large number of Clinical Chemistry or Pharmacological laboratories all over the world. For example in the Netherlands at the moment about 30.000 blood samples are analyzed in over 50 laboratories anually. This estimation is based on available data from a statistical study of pharmacokinetic parameters of anti-epileptic drugs (Guelen et al 1975 and 1977). In the United States over 500 laboratories are known to measure anti-epileptic drug concentrations (Pippenger et al 1978).

In each sample about three different compounds have to be analyzed. Since an average analysis costs approximately Hfl. 125,-- ($ 50,--),one can easily see that large amounts of money are involved in these determinations. This amount of money is payed by social security, health insurences or by patients themselves. Also in view of the high costs attended to the measurements of drug concentrations and the small possibilities to use these values more meaningfully up to now, a critical consideration of the benefit of the plasma concentration measurements is indispensable.

Besides the financial aspects the pharmacological points of view have to be considered. The anti-epileptic drugs show a wide range of efficacy, varying from subtherapeutic to toxic effects at apparent 'normal' dosage regimens. So large inter-individual differences in the plasma concentrations are found in patients treated with the same dose of the drug (Penry 1974),

due to a number of variables.
A number of reasons are indicated why anti-epileptic drugs plasma concentrations should be measured :

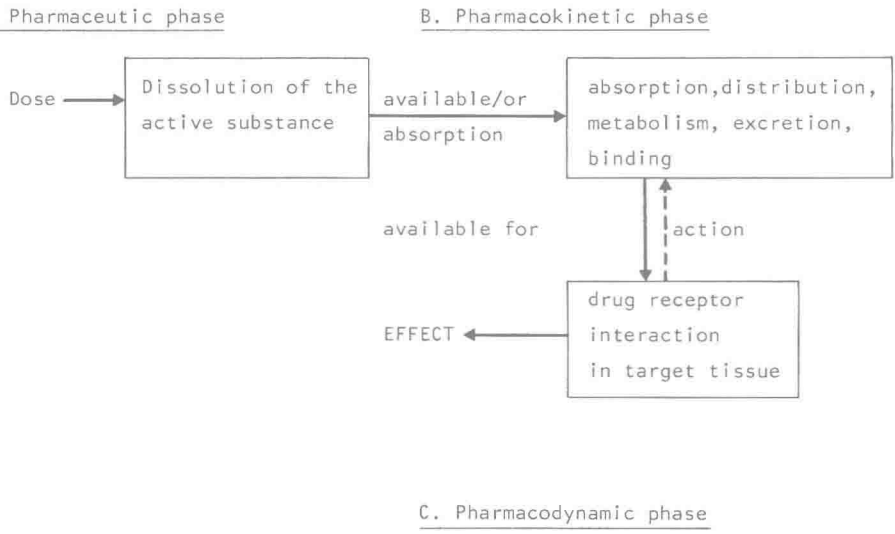
1. Adjustment or correction of an optimum individual dosage regimen in patients responding inadequately at a 'normal dose'.
2. Identification and/or affirmation of a suspected toxicity in patients in which the clinical manifestations can be observed insufficiently.
3. To check the patient's adherance to the prescribed regimen.
4. To identify drug interactions.
5. To find abnormalities in the resorption of the drug, changes in the elimination pattern, failures in metabolism, etc.

The usefulness of plasma concentration monitoring for the various anti-epileptic drugs has been discussed in literature extensively (Woodbury et al 1972, Penry et al 1972, Gardner-Medwin 1973, Penry 1974). In general these findings, in relation to the use of plasma concentration data in the accompaniment of epileptic patients, are positive for the proof of toxicity or crude underdosing. However the problems will be larger when the so-called therapeutic effective concentration has to be established. This subject will be discussed in detail in chapter 2.

CHAPTER 2.

WHY RATIONAL ANTI-EPILEPTIC DRUG THERAPY?

Drugs administered to the body undergo a number of processes which can be rendered in a diagram according :



Depending on a number of factors, like lipophylicity, binding to proteins and tissues, rates of metabolism and elimination, the drug will be distributed all over the body. In practice it means that only a limited part of the active compound administered, finally reaches a place where the effects occur, the receptor. In general, one drug, evokes as many effects as there are receptors for that drug.
In the diagram presented one proceeds on the assumption that there is a direct relation between the dose administered, the concentration reached in the body (or the plasma concentration) and the ultimate effect. This relation is the working hypothesis. How difficult it will be to describe this relation practically will appear.

Depending on the given amount of a drug (the dose), several effects may occur :

Also different effects will occur when a drug in the same dose is administered to several patients, as a result of large variations in the plasma concentrations measured, due to interindividual variations in pharmacological and pharmacokinetic processes.
The range between the minimum effective concentration and the minimum toxic concentration is called the therapeutic (safety) range or therapeutically relevant plasma concentration. The appearance of subtherapeutic and toxic effects in a group of patients, will strongly depend on this therapeutic range.

For a theoretical infinite patient population the therapeutic range is given in figure 1 and 2, for two types of drugs, one with a large therapeutic range and one with a small therapeutic range. In case of a large therapeutic range (figure 1) improvement of the dosage regimen, when subtherapeutic or toxic effects occur, will certainly lead to concentrations of the drug in the body (or plasma concentrations) whereby optimum therapeutic efficacy is reached in 95% of the patient population. Different figures will be reached in case of a small therapeutic range (figure 2). Both toxic and absence of effect are likely to be observed and optimum therapeutic efficacy within one concentration range will never be found for the majority of the patients.
This very last sample is often observed in the accompaniment of epilepsy where symptoms appear to be resistant to drug therapy. Difficulties even will increase for combinations of drugs, as often used in anti-epileptic drug therapy and for drugs with pharmacologically active metabolites, for example Primidone of which approximately 25% is metabolized to Phenobarbital in addition to others.