Therapeutic Drug Monitoring

Edited by
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THERAPEUTIC DRUG MONITORING

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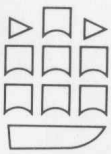

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Preface

Ten years ago few clinical laboratories had any interest in measuring drugs in blood plasma and those that did confined their attention almost exclusively to drug intoxications. All that has now changed and therapeutic drug monitoring has become one of the fastest growing branches of clinical medicine. There are three main reasons for this. The first was the appreciation by an ever-growing number of medical scientists and clinicians that, for a few well-tried drugs, therapeutic response correlated better with the blood drug concentration than with the dose of drug administered. The second was the development of analytical methods, such as gas-liquid and high-pressure liquid chromatography, and radio- and enzyme-immunoassay, that put drug plasma measurements within the capability of any reasonably well-equipped laboratory. The third, and ultimately most important reason, was the educational drive, coupled with the sale of pre-packed kits for making plasma drug measurements, that was mounted by a couple of innovative reagent manufacturers and led to a greater appreciation of the benefit patients could derive from receiving 'tailor-made' rather than 'off-the-peg' therapy.

We felt the time had come to take stock of the situation; to look back at what has been achieved and if possible to look forward into the future without becoming outrageously speculative. This book draws heavily, but not exclusively, upon lectures given at a satellite symposium on therapeutic drug monitoring held in Guildford, England in August 1980 under the auspices of the 1st World Congress on Clinical Pharmacology and Therapeutics. Authors were invited on the basis of their contributions to the knowledge of, and involvement in, the subject matter of their respective topics. The result is the first authoritative book on the current state of the art and science of therapeutic drug monitoring; a truly multidisciplinary subject which not only calls upon the skills of physicians, pharmacologists, chemists and statisticians, but also upon those of clinical biochemists, pharmacists and laboratory reagent manufacturers.

The number of drugs presently known to be worth monitoring represents only a tiny fraction of those being used, every day, in clinics and hospitals throughout the world. Whilst it is unlikely that all, or even a large percentage of them, will ever be shown to repay the cost and effort of measuring them in blood as a guide to effective therapy it is quite certain that many of them will.

A.R.
1981 V.M.

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Table of Conversion Factors

These conversion factors can be used to convert gravimetric to molar units (e.g. 20 μg/ml of phenytoin = 20 × 3.96 = 79.2 μmol/l)

Drug	Molecular weight	Conversion factor
Antibiotics		
Amikacin	585.6	1.71
Gentamicin	Mixture	—
Kanamycin	484.5	2.06
Streptomycin	581.6	1.72
Tobramycin	467.5	2.14
Antidepressants		
Amitriptyline	277.5	3.60
Clomipramine	315.0	3.17
Desipramine	266.5	3.75
Imipramine	280.5	3.57
Maprotiline	281.0	3.56
Mianserin	264.0	3.79
Nomifensine	336.0	2.98
Nortriptyline	263.5	3.80
Protriptyline	263.5	3.80
Zimelidine	315.0	3.17
Antidysrhythmic drugs		
Amiodarone	645.3	1.55
Disopyramide	339.5	2.95
Lignocaine	234.3	4.27
Procainamide	235.5	4.25
Propranolol	259.3	3.86
Quinidine	324.5	3.08
Antiepileptic drugs		
Carbamazepine	236.3	4.23
Ethosuximide	141.2	7.08
Ethotoin	204.2	4.90
Methoin	218.3	4.58
Phenobarbitone	231.2	4.33
Phenytoin	252.3	3.96
Primidone	218.3	4.58
Sodium valproate	143.2	6.98
Antineoplastic drugs		
Cyclophosphamide	261.1	3.83
Cytosine arabinoside	243.2	4.11
Doxorubicin	543.5	1.84
Melphalan	305.2	3.28
Methotrexate	454.4	2.20
Procarbazine	221.3	4.52
5-Fluorouracil	130.1	7.69
Antipsychotic drugs		
Chlorpromazine	318.9	3.14
Haloperidol	375.9	2.66

Table of Conversion Factors (*contd*)

Drug	Molecular weight	Conversion factor
Benzodiazepines		
Chlordiazepoxide	299.8	3.34
Clonazepam	315.7	3.17
Diazepam	284.7	3.51
Flurazepam	395.8	2.53
Lorazepam	321.2	3.11
N-desmethyldiazepam	270.7	3.69
Nitrazepam	281.3	3.55
Oxazepam	286.7	3.49
Temazepam	300.7	3.33
Cardiac glycosides		
Digitoxin	780.9	1.28
Digoxin	764.9	1.31
Miscellaneous		
Paracetamol	151.2	6.61
Salicylic acid	138.1	7.24
Theophylline	180.2	5.55

Contents

1. Serum drug concentrations in clinical perspective

JAN KOCH-WESER

Introduction

From the perspective of a practising physician laboratory tests are useful in proportion to their contribution to more accurate diagnosis or better therapeutic management of his patients. Measurements of drug concentrations in a patient's serum or other body fluids or tissues are no exception. The discomfort to the patient, the commitment of skilled personnel and complex facilities and the costs of such determinations must be justified in terms of more effective and safer pharmacotherapy.

The past decade's experience with determinations of serum drug levels in the clinical setting has been extensive and exciting. It has become clear that in the case of many important drugs information about their concentration in the body is very helpful for their optimal use in certain therapeutic situations. It is equally clear, however, that for other drugs and other clinical settings such knowledge may be totally unnecessary or useless. Finally, there are many drugs for which serum level information is presently of limited clinical value, because the appropriate therapeutic concentration ranges have not yet been defined.

This introductory chapter will review the reasons why the dosage of most drugs should be individualized, the conditions that must be satisfied in order to make information about serum concentrations helpful for dosage individualization, and the many pitfalls and cautions encountered in the use of this information. It is not my purpose to discuss the measurement and interpretation of serum concentrations of individual drugs, since these topics will receive detailed discussion in subsequent chapters of this book.

Individualization of drug dosage

Perhaps no other concept has been as detrimental to good pharmacotherapeutics as that of the 'usual' or 'average' dose. Routine administration of a drug in such a dose can be fully satisfactory only if its therapeutic ratio is so large that one dosage can be efficacious in all patients and excessive in none. This is true of few clinically useful drugs. When given in an unvarying and undiscriminating dosage schedule, most important drugs are ineffective in many patients and cause serious toxic effects in others. When the 'usual' dose is too low for a given patient, the drug may be falsely considered

ineffective in that patient. When it is too high, the patient may be mistakenly considered 'intolerant' to the drug. Alternatively, he may defend himself by silent non-compliance, in which case the result is again an erroneous impression of ineffectiveness of the drug.

In clinical practice the effectiveness and safety of almost all potent drugs can be increased by individualization of their dosage (Reidenberg, 1974). The desirability of individualizing dosage arises from the great individual variation between patients in the relation between the prescribed dosage and the intensity of the pharmacological effect. For some highly effective and toxic drugs the time has indeed come when 'each patient might need an individualized dosage regimen' (Brodie, 1967). However, while the theoretical desirability of adjusting drug dosage to the need and tolerance of individual patients is now widely accepted, its practicality is still questioned by many who take a dim view of the 'realities of clinical practice'.

The argument that individualization of drug dosage is too sophisticated a procedure for the so-called 'average physician' is a patronizing misconception. Practising physicians have long and successfully used drugs like warfarin and guanethidine and have always individualized their dosage. Which practitioner does not routinely and repeatedly determine each patient's dosage requirement of warfarin by measuring the prothrombin time? Nobody refers to the 'usual' dosage of coumarin anticoagulants. The range of prescribed warfarin dosages is as wide as it needs to be in order to achieve in each patient the desired range of prothrombin time prolongation (Fig. 1.1). In the case of guanethidine the best daily dosage for a given patient is determined by titrating the dose against the patient's blood pressure response and undesirable side effects. Again, the maintenance doses prescribed reflect individualization and vary almost hundredfold (Fig. 1.2). It should be obvious to anyone that such a drug could not even be used in therapy unless physicians were capable of individualizing dosages.

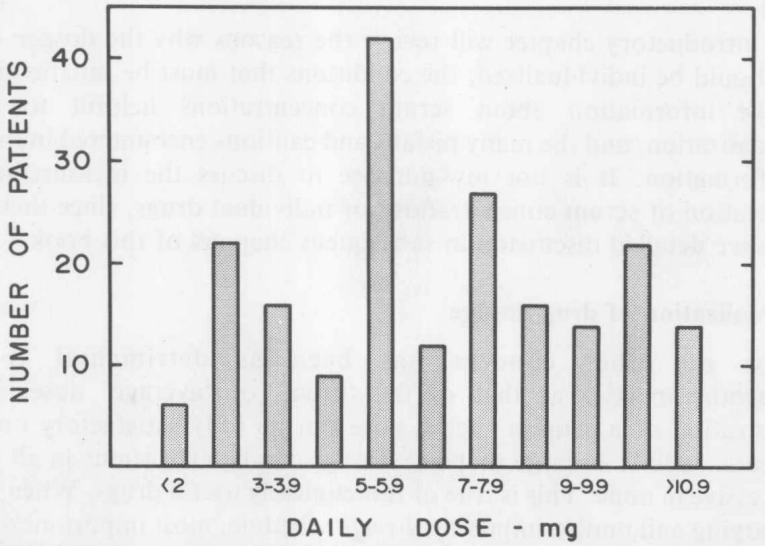

Fig. 1.1 Warfarin dosages prescribed for chronic anticoagulation to 200 ambulatory patients at the clinics of the Massachusetts General Hospital during 1970-1972.

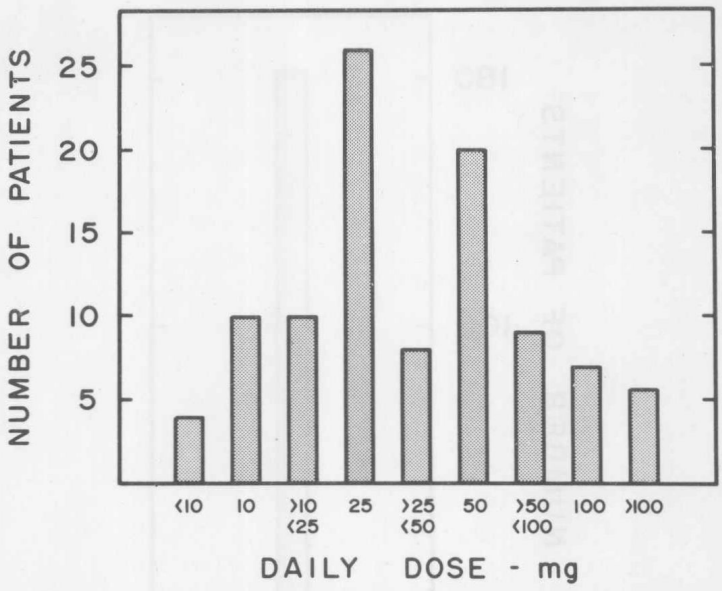

Fig. 1.2 Guanethidine dosages prescribed to 100 ambulatory hypertensive patients at the clinics of the Massachusetts General Hospital during 1970-1972.

Physicians almost always individualize drug dosage when the intensity of the pharmacologic action of a drug is readily established in clinical practice. Such 'titration by patient response' is the simplest, most effective and only completely reliable way to determine individual drug dosage requirements. In addition to anticoagulants and antihypertensives, it is applicable to drugs such as analgesics, hypnotics, diuretics, vasopressors, hypoglycaemics, hypolipidaemics, and many hormones. For other drugs it can be used easily only in specific clinical situations, as when cardiac glycosides are given to slow the ventricular rate in patients with atrial fibrillation or when antiarrhythmic drugs are given with the sole purpose of suppressing frequent ventricular ectopic beats. To be sure, even when 'pharmacologic endpoints' are available in the clinical situation, the dosage of certain drugs is not yet as universally individualized as it should be. This may reflect the fact that in the case of some drugs close clinical observation and careful judgement are required for adjusting the dose to the individual.

Unfortunately, there are many drugs and clinical settings for which patient response is not a constantly available or reliable guide to optimal dosage. The intensity of the pharmacologic effect of such drugs cannot be readily quantified in clinical practice. Anticonvulsant drugs used for prophylactic purposes offer an excellent example. At the beginning of the seventies phenytoin for the prevention of seizures was almost routinely prescribed in the 'usual' dose of 300 mg per day (Fig. 1.3). This remained true even though it had been clearly shown that this dose confers little seizure protection to many patients and causes toxic disturbances of central nervous system function in many others (Kutt & McDowell, 1968). The reason why phenytoin dosage was so seldom individualized was not that it did not need to be, but that it was difficult to do so by clinical criteria. Since many patients had seizures rarely or

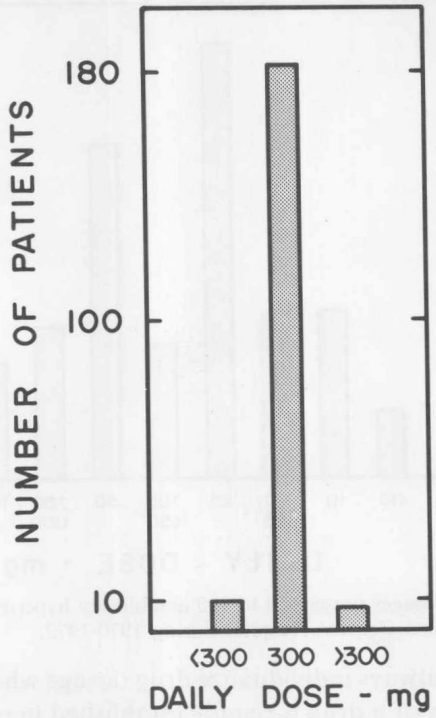

Fig.1.3 Phenytoin dosages prescribed for seizure prevention to 200 ambulatory patients at the clinics of the Massachusetts General Hospital during 1970-1972.

with very variable frequency, the clinical benefit of the usual dosage was often difficult to determine. Even when the therapeutic goal was clearly not being reached with the usual dosage, physicians often added or switched to another anticonvulsant rather than attempting to find the optimal dosage of phenytoin for the particular patient.

Similar difficulties confronted physicians attempting to individualize dosages of many other therapeutic agents. Cardiac glycosides, antiarrhythmics, anti-inflammatory agents and many psychoactive drugs were commonly prescribed in non-individualized dosages. Suboptimal therapeutic or toxic effects were the unhappy results in many patients. During treatment with drugs such as digitalis, quinidine or tricyclic antidepressants it was often difficult to decide on clinical grounds alone whether an unsatisfactory therapeutic response was due to administration of too little or too much of the compound. In this situation many pharmacotherapists began to look for objective and quantitative information that might help to determine the most appropriate dosage of such drugs for a given patient.

Serum drug concentrations in individualization of drug dosage

The need to individualize drug dosage arises from differences between patients in the relation between the amount of drug prescribed and the intensity of effect of the drug at its sites of action. The four steps determining this relationship are schematically illustrated in Fig. 1.4. It is obvious from this figure that determination of serum drug levels for guidance to appropriate

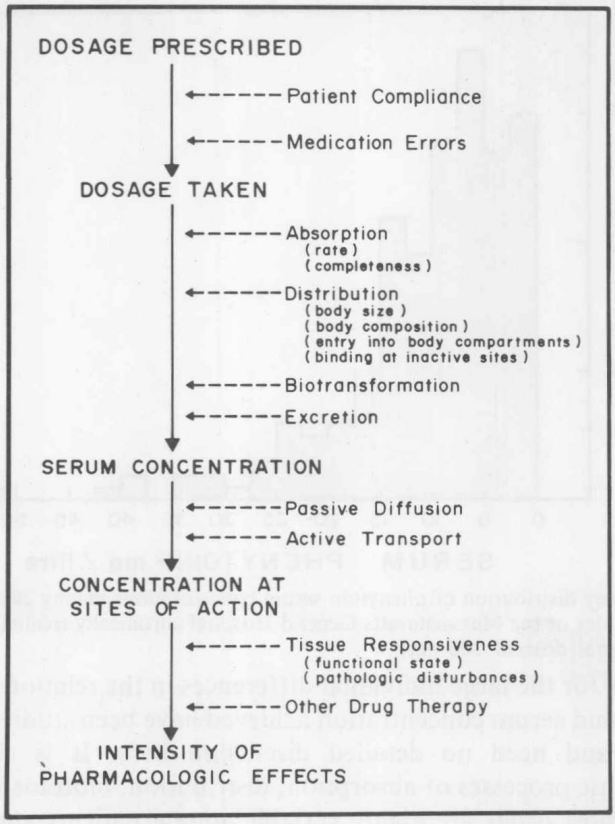

Fig. 1.4 Factors which influence the relation between prescribed dosage and intensity of effects of a drug during clinical therapy.

dosage can be useful only if the main causes for inter-patient variations in the dose-effect relation lie prior to the last two steps. This is indeed the case for most drugs. Individual differences in drug metabolism (absorption, distribution, biotransformation, excretion) are often enormous and usually account for most of the differences in the dose-effect relation. This was stressed 13 years ago by Dr. Bernard B. Brodie in his Albert Lasker Basic Research Award Lecture who called attention to the great heterogeneity of the human species with regard to drug metabolism and suggested that these differences would make it useful to relate drug effects to plasma levels rather than to dosage (Brodie, 1967). The last decade has amply supported this view.

Tenfold or greater differences in the steady-state serum concentrations have been found among patients treated with the same dosage of many important drugs. One example which is by no means unusual may suffice. Fig. 1.5 illustrates that the usually prescribed daily dosage of phenytoin produced the serum concentrations most desirable for anticonvulsant activity (10–20 mg per litre) in only 28.5 per cent of patients. Suboptimal concentrations were present in 60 per cent and potentially toxic levels in 11.5 per cent of the subjects.

Enormous variations among patients in the dose-concentration relation have also been found for digoxin, hydralazine, phenothiazines, perhexiline, propranolol, tricyclic antidepressants and many other drugs.

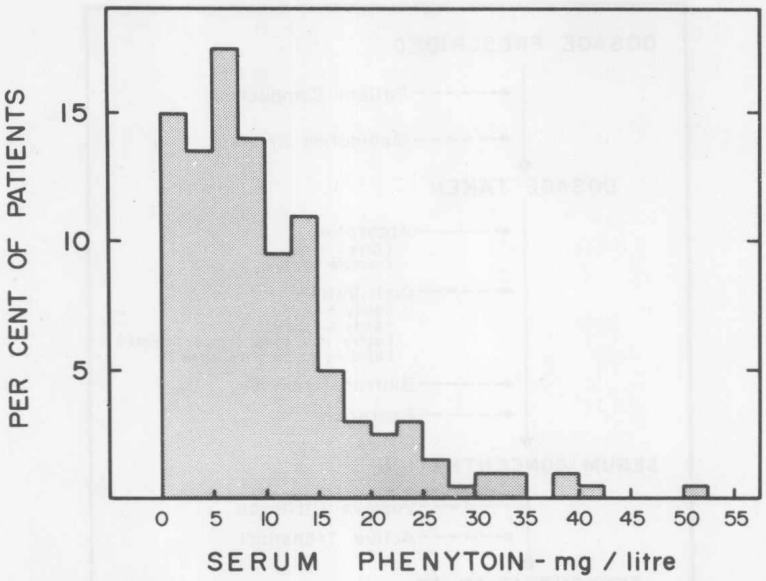

Fig. 1.5 Frequency distribution of phenytoin serum concentrations among 200 ambulatory patients at the clinics of the Massachusetts General Hospital chronically treated with a prescribed daily oral dose of 300 mg.

The reasons for the large individual differences in the relation between dose administered and serum concentration achieved have been studied in detail for many drugs and need no detailed discussion here. It is clear that the pharmacokinetic processes of absorption, distribution, biotransformation and excretion of most drugs are highly variable among patients and in the same patient with time (Vesell, 1971). They are influenced both by the genetic make-up of the individual and by a host of environmental factors, including the effects of disease and of concomitant administration of other drugs (Vesell, 1974; Koch-Weser, 1975a).

Pharmacokinetic differences among patients are inevitably reflected in the serum drug concentration achieved with any given drug dosage. To the extent that these differences are responsible for individual variations in the dose-effect relationship, knowledge of the serum concentration will help in appropriate individualization of drug dosage. Thus, one can predict a priori that the clinical effects of therapy with many drugs must correlate better with the serum concentration achieved than with the dosage prescribed (Koch-Weser, 1975a).

While the serum concentration-effect relation is for many drugs far more predictable than the dose-effect relation, this obviously does not mean that the former is the same for all patients and at all times (Koch-Weser, 1972, 1975a; Smith & Rawlins, 1973; Ariëns, 1974; Azarnoff, 1974). The serum concentration of a drug in a given patient cannot possibly indicate the intensity of the drug's therapeutic or toxic actions with complete precision since two important steps lie between them (Fig. 1.4). At best one can define the usual range of therapeutic concentrations. Some overlap of these with subtherapeutic and toxic concentrations is inevitable. The extent of this overlap varies depending on the drug and the clinical situation. For some drugs

it can become so great that the serum concentration is no longer a useful guide for dosage individualization.

Value of serum drug determinations

Determinations of the serum concentration of all drugs can be useful in the management of intoxications, for the detection of non-compliance or surreptitious use, and in bioavailability studies. Their value is far less uniform in pharmacotherapy.

The concept of using serum drug levels for guidance in pharmacotherapy has become embroiled in a rather pointless controversy. As is true of many sound concepts, it has suffered almost as much from the unrealistic and over-enthusiastic claims of uncritical boosters as from the carping of sceptics. The former have made claims concerning patient care that no laboratory measurement can ever live up to when it is divorced from careful medical observations of the patient, is not integrated with everything else that is known about him and is not interpreted with professional judgement. The latter have devoted much time and ink to the knocking over of straw men. Certainly routine determinations of serum concentrations of all drugs are not the sine qua non of good patient care. Drugs can be and were used effectively without any knowledge of their concentration in the body, and determination of serum concentrations does not guarantee skilful pharmacotherapy. What are the conditions that must be fulfilled in order to make determinations of serum drug concentrations useful in clinical therapy? Broadly speaking, drugs fall into 5 categories in terms of how valuable knowledge of serum concentrations is to the practising physician. These are listed in Table 1.1 and discussed in some detail in the following paragraphs.

Table 1.1 Clinical value of knowing serum levels of specific drugs

1. *Unnecessary* when dosage need not be individualized.
2. *Unnecessary* when intensity of pharmacologic effects can be clinically quantitated.
3. *Useless* when serum concentration is not predictably related to intensity of pharmacologic effects.
4. *Not yet useful* when concentration-effect relation remains undefined.
5. *Useful* when therapeutic range of serum concentrations has been established.

It should be obvious that there is rarely any need to measure serum levels of drugs whose dosage need not be individualized. However, such drugs must have an enormous therapeutic margin. They are few and far between if one disregards those that are in actual fact given as placebos. The list does not include much beyond some vitamins or certain penicillins when used in the treatment of highly susceptible bacterial infections.

Even when dosage individualization is desirable, it is generally unnecessary to determine serum levels of drugs whose intensity of action is readily monitored in clinical practice. Good clinical endpoints are intrinsically superior to serum concentration information. In this connection warfarin and guanethidine have already been mentioned. What is true for guanethidine applies to almost all antihypertensive drugs (Koch-Weser, 1980). Since the pharmacodynamic determination of the magnitude and duration of action of