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Contemporary Issues in Clinical Biochemistry

Therapeutic Drug Monitoring

Edited by

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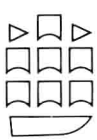

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Therapeutic Drug Monitoring

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Preface

An effective therapeutic drug monitoring service is founded on good analytical practice and the efficient organisation of laboratory resources. At the same time the clinical chemist must acquire a background knowledge of the pharmacological and toxic properties of the drugs measured, of their metabolism and distribution and how these are influenced by factors such as age and disease states. By so doing he is best able to assist the physician in interpreting the analytical findings for an individual patient. This book, which has brought together a number of experienced workers in the field, offers guidance on all these aspects of therapeutic drug monitoring. It is my hope that it will help all those involved in this area of laboratory medicine and that patients will thereby benefit.

1985 B.W.

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General aspects

A historical introduction

Medicines and nostrums have played a central role in the treatment of disease since time began. It is, however, only comparatively recently that their use has been based on a knowledge of their pharmacology. With a few notable exceptions, e.g. opium, quinine and digitalis, the medicaments employed by the therapists of yesteryear — whether they were witch-doctors, apothecaries, pharmacists or 'registered' physicians — were unpleasant, noxious or overtly poisonous substances one of whose main functions were to supplement the mysticism which surrounded, and was the hallmark of, the therapist or doctor (Haggard, 1950; Ackerhnecht, 1973). The acute toxic effects produced by such 'medications' included vomiting, purging and scouring all of which were considered to contribute to the healing process. They were endowed with magical healing properties despite the complete absence of supportive evidence of efficacy which was considered neither attainable nor, indeed, desirable. Only during the last two or three decades of the 19th century, with the application of scientific method to the study of biological mechanisms in general and of physiology and pharmacology in particular, did the art and science of therapeutics progress beyond that practiced for the whole of the preceding millenium or longer. A typical pharmacopeia of the first part of the present century was scarcely different from one produced 400 years before, in contrast to one produced today to which it would bear no resemblance at all. Barely a dozen drugs mentioned in the earlier pharmacopias find a place in the current national formulary even such novel and, for their time, 'wonder' drugs as salvasan and neosalvasan, antipyrine, phenacetin and barbitone having been assigned to antiquity because of their now unacceptably high toxicity relative to their low efficacy.

Disillusionment with drug therapy for disease and the high incidence of morbidity and even mortality associated with it led to the development during the 18th and 19th centuries of various types of 'alternative medicine' of which homeopathy was, and still is, the best known and most successful. If the theory upon which it was based was both naive and scientifically unsound practitioners of homeopathy did at least avoid poisoning their patients. It was not completely in jest that the 18th century wit William Seward wrote 'a doctor is defined to be a man whom we hire for the purpose of telling stories

in the chamber of a sick person till nature effects a cure or his medicine kills the patient'. The lessons of history have, however, not been well learned and everyday patients die or are crippled as a result of the misuse of drugs by medical practitioners and others. These are in addition to those who are unfortunate enough to suffer adverse side-effects that result from the calculated risk taken whenever a drug is prescribed no matter how safe it is considered to be. These need not be fatal or even permanently damaging to be clinically important. They are a major factor in non-compliance (Porter, 1969; Blackwell, 1972, 1973) now recognised as one of the main reasons why pharmacologically active drugs properly indicated and prescribed, fail to exert their expected therapeutic effects (Sackett et al, 1975).

It has long been customary to adjust the dosage of drugs — at least those which rely upon their pharmacological rather than toxicological properties for their clinical usage — to suit individual patients. This was achieved by monitoring their pharmacodynamic effects and increasing or decreasing the dose accordingly. Thus digoxin was 'individualised' by counting the pulse rate and/or enquiring about the presence and severity of undesirable side effects; the dose of salicylates was increased in the treatment of rheumatic fever until dose-dependent side-effects, notably tinnitus, appeared and then slightly decreased in order to produce maximum therapeutic benefit with minimum or zero toxicity; in the treatment of diabetes insulin dosage was increased until the blood glucose concentration fell within the normal reference range for at least the major part of the day; antihypertensives were given in increasing dosage until the desired effect upon blood pressure was produced or toxic effects, especially postural hypotension, became troublesome. It was, however, appreciated that this method of adjusting dosage was not applicable to all, or even to many, drugs and in any event was time consuming and dependent upon good clinical judgement.

The idea that the treatment of diseases by drugs might be improved by measuring their concentration in blood and adjusting the dosing regime in order to bring the concentration within a pre-determined (optimum therapeutic) range is a comparatively new one (Brodie & Reid, 1971; Koch-Weser, 1972; Prescott, 1972; Vesell & Passanti, 1971; Marks et al, 1973) and in its present form dates back no further than the early 1970s. It owes its origins to the confluence of various conceptual and technological advances which had themselves been developed only during the preceding two decades. Of these developments the most important were (1) the amalgamation of three ancient disciplines of pharmacy, material medica and academic pharmacology, into a single new one of clinical pharmacology; (2) an interest in, and understanding of, the biochemistry of xenobiotics and of drug metabolism (Williams, 1947; Parke, 1968); (3) the discovery of pharmacogenetics as a major determinant of drug responsiveness in man (Vogel, 1959; Kalow, 1962; Evans & Clarke, 1961) and finally (4) the availability of a variety of new analytical procedures that removed blood drugs measurement from an exclusively research arena to a practical and clinically available one.

CLINICAL PHARMACOLOGY

This is the name suggested by Gold (1952) to describe a new discipline which is concerned with the effectiveness of drugs in man.

Properly designed, controlled clinical trials of the therapeutic effectiveness of drugs were first introduced in the UK shortly after the second world war (Hill, 1960), and heralded the beginning of the demise (still unfortunately not complete) of drug use based on anecdotal and/or uncontrolled evidence of efficacy. One of the first drugs to be subjected to detailed scrutiny was streptomycin, the first antibiotic shown to be useful in the treatment of tuberculosis. As a result of nationwide controlled clinical trials it was established that streptomycin was effective in curing a large proportion of patients afflicted with tuberculosis even though a small percentage of them suffered permanent neurological damage — a large but nonetheless acceptable price to pay for cure of a grave and frequently fatal disease (Daniels, 1951). Subsequently other drugs were subjected to similar scrutiny. For some it was observed that a favourable clinical response correlated better, in retrospect, with the concentration of drug in the blood than with the dosage of drug administered and that contrary to expectations these often bore little relationship to each other.

The concept of reversible drug-receptor interactions was introduced by Clark (1933) to explain dose-dependent tissue responses and was developed by Paton (1961). It was consistent with, and explanatory of, the better correlation between therapeutic effectiveness and plasma concentration than with dosage of a drug alone. It was, however, observed only with some and not all drugs, the latter being designated 'hit-and-run' because their effects were thought to be due to irreversible changes produced by the drug upon cells rather than to its persistance in the body.

The causes of poor correlation between plasma levels and drug dosage have been elucidated as a result of studies of their absorption, distribution and elimination, made possible by improvements in analytical technology. Studies of this type were initially undertaken by biochemists and clinical pharmacologists using experimental animals and human volunteers. They were generally made under research rather than clinical conditions and their mathematical expression was referred to as pharmacokinetics.

It is now widely accepted that pharmacokinetics — put crudely as what the body does to drugs in contrast to what drugs do to the body, which is generally referred to as pharmacodynamics — had its origins in two papers published by Teorrell in 1937. The first textbook on what would now be called pharmacokinetics was published in 1953 (Dost, 1953) but not until some 8-10 years later, coinciding with the widespread recognition of clinical pharmacology as a scientific medical discipline, did interest in it extend beyond a small circle of cognoscenti.

One of the most important concepts to emerge from pharmacokinetic studies was that of the plasma 'steady state' drug level which is central to the

rationale of therapeutic drug monitoring. Later, and only following epidemics of phenytoin and digoxin toxicities which occurred in Australia and worldwide respectively and were consequent upon changes in formulation, did the concepts of bioequivalence attract widespread attention (Brodie & Heller, 1971). Previous attempts to engender interest were based mainly upon clinical observations rather than upon blood drug measurements and had frequently been greeted with ridicule. Other pharmacokinetic parameters such as volume and rate of distribution, protein-binding, site and nature of drug metabolism and elimination became the subject of intense review during the decade 1960-1970, culminating in a major symposium at the New York Academy of Sciences in 1970. This was subsequently published as a large volume in the *Annals of the New York Academy of Sciences.*

DRUG METABOLISM

The mechanisms by which the pharmacological effects of drugs are brought to an end have been discussed for many years. It is, however, only in the past half century that the importance of their biodegradation prior to excretion in the urine and bile has been appreciated. The pioneering work of Techwyn Williams (1947) on detoxication mechanisms marked at the beginning of biomedical interest in drug metabolism and its role in clinical pharmacology. One consequence of his work and that of his pupils (Parke, 1978) was recognition that metabolic conversion of drugs by phase I metabolic reactions can lead to the formation of pharmacologically active metabolites just as readily as to pharmacologically inactive ones. This is in contrast to phase II (conjugation) reactions which almost invariably produce water-soluble inactive compounds. Another was of the enormous differences in the way various species — sometimes even closely related ones — handle drugs. This has enormous implications both for the pharmaceutical industry and drug regulatory bodies which now recognise — albeit reluctantly — that animal studies alone cannot provide all the information necessary before a new drug can be released freely with complete safety onto the market.

PHARMACOGENETICS

The enormous interspecies difference in drug metabolism observed in experimental animals found its parallel, in man, with the introduction of drugs such as isoniazid, succinyl-choline and sparteine. These revealed the existence, within the healthy community, of individuals who could be classified into two or more sub-populations on the basis of their ability to detoxify (biodegrade) the drug. In the case of isoniazid roughly half the population to whom the drug was given for the treatment of tuberculosis failed to derive the expected benefit. This was shown to be due largely to their failure to establish a minimum inhibitory concentration of the drug in the plasma and itself due to rapid acetylation and excretion of the drug preventing its accumulation in

the body. In the case of succinyl-choline, patients treated with the usual dose failed to recover muscular power normally after it had been given to produce muscular relaxation during surgical operations. They subsequently either required artificial ventilation until their power gradually and spontaneously recovered, or they died (Evans et al, 1952). Later shown to be due to the inheritance of a pseudocholinesterase isoenzyme varient with an inability to detoxify (biodegrade) succinyl choline by hydrolysis (Lehmann et al, 1961), this disorder provided an archetypical model of pharmacogenetic disease, i.e. one resulting from the administration of a drug to a subject with a genetically determined difference in drug metabolism from the majority of the population.

The term pharmacogenetics was coined by Vogel in 1959 and was the subject of a monograph published only 3 years later by Kalow (1962). With the greater interest in measuring blood drug concentrations that followed the introduction of improved analytical techniques it soon became apparent that, for most drugs, there were large interpersonal differences in rates of metabolism leading to wide variations in steady state plasma drug levels and in therapeutic effectiveness in patients treated with similar drug dosage regimes. These differences were recognised as being at least partly genetically determined (Vesell & Page, 1968) although environmental factors were also important.

BLOOD DRUG MEASUREMENTS

The detection and measurement of drugs in biological fluids has been employed by forensic scientists and toxicologists since long before the modern era of laboratory medicine. They played little part in clinical practice, however, until the mid-1960s when the fruits of analytical methods developed during the preceding two decades became available to clinical workers. Previously they had had to rely largely, if not exclusively, upon analytical techniques which were either too expensive, slow, technically demanding and insensitive to make them clinically useful or else required the use of specially prepared isotopically labelled variants of the drug which could be used to measure its concentration in blood and other body fluids in healthy volunteers and selected patients in the course of academic pharmacokinetic studies. It was, nonetheless, with the aid of such techniques that most of the useful knowledge relating 'steady-state' blood levels to their toxicity and therapeutic effectiveness was built up. This data base still provides much of the information upon which current therapeutic drug monitoring is founded, comparatively little of which has been generated in the recent past despite the enormous advances in analytical technology that have taken place during this time.

Within a short period between 1970-1973, several critical reviews were published (Brodie & Reid, 1971; Koch-Weser, 1972; Marks et al, 1973; Prescott, 1972; Vesell & Passanti, 1971) which, though based upon discon-