DRUGS
FOR HEART DISEASE

Edited by
John Hamer

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Preface

This book reviews the clinical pharmacology of cardiovascular drugs. I have started from the premise that 'clinical pharmacology' is the scientific study of the use of drugs in man. It is inevitably necessary to refer to much basic work in animals as it is not technically feasible to investigate drug actions on the myocardium at a cellular level in man, or ethically acceptable to use invasive methods to study drug action in patients unless opportunities arise during diagnostic investigation. I have sought to avoid the detailed consideration of mechanisms derived from animal pharmacology, but to draw on animal work for features helpful in the understanding of the response of human disease to treatment.

The apparent remoteness of animal pharmacology from clinical practice is in part responsible for the emergence of Clinical Pharmacology as a new independent discipline with immediate relevance to the treatment of patients, and it is this aspect of pharmacology I am seeking to emphasize in relation to my experience as a clinical cardiologist. In numerical terms, cardiovascular disease forms half of medicine and it is hoped that the book will be of interest to general physicians as well as to specialist cardiologists and trainees.

The early activity of clinical pharmacology has been connected with the development of techniques to measure drug concentrations in blood and other biological fluids. This development has led to a close concern with 'pharmacokinetics', i.e. the way drugs are handled in the body, and is dealt with in the first two chapters which outline the advantages of measuring drug blood levels and the techniques in current use; it is hoped that this section will be helpful to physicians planning to set up such a service. Blood level measurements lend themselves to the study of pharmacokinetics, including the comparison of different formulations of

a drug (bioavailability), and to the study of drug interactions. Although a knowledge of how drugs are handled in the body is fundamental to their sensible use in treatment, I hope to avoid the impression that blood level measurement is the essential basis of the discipline.

Clinical pharmacology is primarily concerned with the selection of appropriate therapy, and adjustment of dose and administration of drugs to the needs of the patient. I have attempted to consider the mechanisms of drug action, the absorption, metabolism excretion of drugs (pharmacokinetics); the effects of the drugs in man (pharmacodynamics), and the rational use of the drugs in disease, including interactions with other drugs and toxic effects.

I have attempted to marshall and synthesize the often contradictory reports from the continuously growing medical literature to give a picture of the current state of therapeutics in the light of my experience as a clinical cardiologist in academic, hospital and private practice, and as an undergraduate and postgraduate teacher both in England and in the United States. My early experience as a registrar to both William Evans and Clifford Hoyle, who showed the way with a sound study of drugs for angina, gave me a healthy scepticism about the effects of drugs in heart disease, which subsequent contact with the pharmaceutical industry has failed to eradicate, although it has helped me to appreciate the problems of the development of new drugs and their introduction into therapeutics. I was personally fortunate to be early in the field when beta-blockers appeared and comparative studies have led to a continued interest in anti-arrhythmic drugs.

This is something of a Bart's book and I am particularly grateful for outside help with the hypertension chapter from my friends of the Wellcome Foundation. I seek understanding from authors who will feel that insufficient prominence is given to their research and from pharmaceutical companies who may consider the advantages of their drugs inadequately described. If many doctors handle drugs badly the fault must lie in part with their training. It is my aim to correct such faults in my own field and to expiate my previous sins in this respect.

London John Hamer
November, 1977

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Contents

I

The Principles of Clinical Pharmacology Applied to Heart Disease

A—Indications for Measurement of Cardiac Drugs

PAUL TURNER

AND

CLIVE M. KAYE

The development of a powerful and accurate methodology for estimating drugs and their metabolites in body fluids has made popular their measurement in a wide variety of conditions (Jellett, 1976).[1] However, the clinical value of such estimations has not yet been fully assessed, but is probably of greatest importance in those situations where (a) the therapeutic blood level is in a narrow range above which serious toxicity usually occurs and below which the drug is usually ineffective, and (b) wide variation in blood levels is found after standard dosage. Furthermore, such estimations assume a direct relationship between the blood level and therapeutic or toxic effects of a drug. In other words, it is assumed that the concentration of drug in the blood is directly

related to that in the tissues when equilibrium or 'steady state' has been reached. In the case of drugs acting on the heart, it is the myocardial concentrations which are important, although, of course, brain concentrations may be important if a drug has central actions which modify cardiac function. There are great practical and ethical difficulties involved in demonstrating such correlations between blood and myocardial concentrations in man, but it has been achieved for digoxin (Güllner *et al.*, 1974). Significant correlations had previously been demonstrated in dogs between the electrophysiological action of digoxin and its serum concentration (Barr *et al.*, 1972; Malcolm and Coltart, 1977) and in man between digoxin plasma concentrations and the ventricular rate in atrial fibrillation (Chamberlain *et al.*, 1970).[2,3]

There are many factors which give rise to the observed variation in blood level following administration of standard doses of a drug to man.

1.1 Formulation

Many physicians still do not appreciate that when they prescribe a drug the patient actually receives a medicine. The active substance which is prescribed may represent only a small proportion of the total weight of an oral solid dosage form, such as a tablet or capsule. Similarly, the form of a drug for injection requires solution or suspension in a fluid vehicle of varying complexity. It is now realized that the other constituents of dosage forms are not necessarily 'inert' but may play an important part in facilitating or hindering the absorption of a drug, and that appropriate manipulation of such materials may permit the development of sophisticated delivery systems for delayed or selective release of the drug within the gastro-intestinal tract. The following are some of the more important factors which are invoked in the production of tablets and capsules which may influence a drug's absorption (Curry, 1977):

(*a*) Diluents, such as lactose or calcium sulphate, to increase bulk. Their importance was demonstrated by an outbreak of phenytoin intoxication when the formulation was changed from one to the other (Tyrer *et al.*, 1970).

(*b*) Granulating and binding agents, such as tragacanth, syrup and bentonite, which assist aggregation of the powder into granules to permit compression into tablets. Boman *et al.* (1975) have shown that bentonite adsorbs rifampicin rapidly and strongly, and so can decrease significantly the absorption of rifampicin if given simultaneously, for example, in PAS granules in which it may be used to aid granulation.

(*c*) Lubricants, such as talc, to prevent granule adherence to the tablet punches.

(*d*) Disintegrating agents which are incorporated to produce rapid tablet disintegration in the gastro-intestinal tract. They include substances, such as starch, which swell on contact with moisture, and mixtures of sodium carbonate and tartaric acid which effervesce on contact with moisture. The latter agents may well influence solution or absorption of weak acids or bases by their effect on the pH of the immediate environment of the drug particles.

(*e*) Coating materials, such as sugar, which prevent disintegration before the tablet reaches the stomach or intestine.

(*f*) Envelopes of gelatin to produce capsules, in which granulating agents are not required. It is a common misconception that drugs are released more readily from capsules than from tablets, but this is not necessarily true. It has been shown with several drugs, including hydrochlorothiazide and triamterene, that their absorption was greater from tablet formulations than from capsules (Tannenbaum *et al.*, 1968).

(*g*) Special formulations employ complex pharmaceutical manoeuvres to control disintegration and dissolution rates, so regulating the rate of absorption of a drug. For example, the standard formulation of procainamide (Pronestyl) needs frequent administration at 4–6 hourly intervals (Koch-Weser *et al.*, 1969) to provide and maintain adequate plasma levels which should be monitored (Shaw *et al.*, 1974), but sustained release forms now available, require only 8-hourly administration (Fremstad *et al.*, 1973; Karlsson, 1973; Ruosteenoja *et al.*, 1973; Graffner *et al.*, 1975; Shaw *et al.*, 1975).

As well as these non-drug factors, it is important to remember that different manufacturing processes may result in the production of different physical forms of the active drug. The absorption of digoxin, for example, is markedly affected by particle size (Shaw *et al.*, 1973), and this may have contributed to the differences in bioavailability demonstrated between two different types of Lanoxin tablets (Falch *et al.*, 1973).

1.2 Absorption

The absorption of drugs administered orally takes place mainly in the small intestine, and it is not surprising, therefore, that drugs which alter the rate of gastric emptying may modify the rate of absorption of other drugs.[4] For example, tricyclic antidepressant drugs produce an increase and metoclopramide a decrease in serum digoxin levels (Manninen *et al.*, 1973). Oral hyoscine has been shown to delay the absorption of propran-

olol (Kaye *et al.*, unpublished observations).[5,6] Whether or not an increase or decrease in gastric emptying rate increases or decreases the rate of absorption of a particular drug cannot be predicted with certainty, as it depends on several other factors including the drug's solubility and site of absorption.[6,7]

Malabsorption states arising from mucosal disease or from intestinal hypermotility have been shown to produce lower steady-state serum levels of digoxin (Heizer *et al.*, 1971; Parsons, 1977).

1.3 Hepatic clearance

Cardiac drugs which are mainly eliminated by the hepatic route may require modified dosage in patients with liver disease (Klotz, 1976).[8] The plasma elimination of lignocaine is reduced in patients with advanced alcoholic liver disease (Thomson *et al.*, 1973). This may be due to changes in liver blood flow (Stenson *et al.*, 1971) or to decreased metabolic activity, since it has been shown that lignocaine metabolism is reduced in liver disease (Adjepon-Yamoah *et al.*, 1974).[9] See Section 2.13.5.

Liver enzyme induction associated with treatment with a variety of drugs, such as barbiturates and phenytoin, might be expected to increase hepatic elimation of susceptible cardiac drugs. Although there is a tendency for fewer clinicians now to use barbiturate drugs, even in the management of epilepsy, phenytoin is used as an antiarrhythmic agent, and it should be remembered that it may induce its own metabolism as well as that of other cardiac drugs, which are mainly eliminated by the liver, if used for more than 10–14 days. Solomon and Abrams (1972) found that the plasma concentration of digitoxin may be reduced by as much as 50%, if phenobarbitone is also being administered.

The hepatic clearance of some drugs, for example propranolol, is very high (Evans *et al.*, 1973). In this particular case, an active metabolite, 4-hydroxypropranolol, is formed and, as a result, the relationship between pharmacological activity and plasma level of unchanged propranolol after oral administration is markedly different from that after intravenous administration of propranolol (Coltart and Shand, 1970; Cleaveland and Shand, 1972).[10]

1.4 Renal excretion

Impairment of renal function leads to a retention of drugs which are mainly eliminated by the kidneys and so may require a modification of dosage. Prediction of dose from indices of renal failure has been attempted (Dettli, 1976; Bennett *et al.*, 1977). Among the cardiac drugs which have been shown to be influenced by renal impairment and require a reduced dosage are the more water-soluble beta-blockers, such as practolol

(Eastwood *et al.*, 1973; Bodem *et al.*, 1974; Harvengt *et al.*, 1975; Kaye *et al.*, 1975), procainamide (Weily and Genton, 1972) and digoxin (Jelliffe *et al.*, 1972; Koup *et al.*, 1975). The elimination of lignocaine (Thomson *et al.*, 1973), phenytoin (Letteri *et al.*, 1971), propranolol (Thompson *et al.*, 1972; Lowenthal *et al.*, 1974) and quinidine (Kessler *et al.*, 1974) do not appear to be substantially changed by renal disease, probably because their main route of elimination is hepatic rather than renal.[11,12]

The pharmacokinetics of drugs in renal disease is reviewed by Lowenthal (1977).[13] The volume of distribution of drugs may appear to be changed in severe renal failure. Reuning *et al.* (1973) showed this for digoxin and suggested that a decreased loading dose should be given to patients in this condition.[14] The effect is probably related to changes in plasma and tissue protein binding which are known to occur with several drugs in renal failure (Andreasen, 1973; Reidenberg *et al.*, 1971; Mussche *et al.*, 1975). Even blood collection methods may alter the protein binding of a drug; this has been reported to have given spuriously low plasma propranolol levels during one study (Cotham and Shand, 1975).

The rate of elimination of weak acids and bases may be markedly dependent on changes in urine pH (Milne *et al.*, 1958; Weiner and Mudge, 1964). This has been demonstrated for mexiletine, where a mean plasma elimination half-life of 2.8 hours was found, when urine pH was maintained at about 5, and of 8.6 hours at a urine pH of 8. It is of interest that estimations of urine pH in patients in a coronary care unit ranged from 4.4 to 6.8 over a 24 hour period (Kiddie *et al.*, 1974).

1.5 Age

Although cardiac drugs are frequently prescribed for elderly patients, little information is available to the physician to enable the influence of age on drug absorption, distribution and elimination to be considered. It is, perhaps, paradoxical that the elderly are the largest section of the population receiving regular drug treatment, but most of the kinetic information on the drugs they receive is based on studies in young patients or volunteers.

Creatinine clearance falls with advancing age (Shock, 1946) and this may lead to accumulation of drugs such as digoxin which are excreted mainly through the kidneys (Bayliss *et al.*, 1972; Collste and Bergman, 1976). See Section 4.12. Castleden *et al.* (1975) found that a small oral dose of propranolol produced higher plasma levels of unchanged drug in elderly than in young subjects and suggested that this reflected a reduced first-pass hepatic clearance in the elderly. Several different factors may operate to influence drug kinetics in the elderly patient (Trounce, 1975; Nation *et al.*, 1977). Estimation of plasma levels may, therefore, be

particularly helpful as a guide to treatment (Beck and Vignalou, 1975). Similarly, serum digitoxin or digoxin levels may serve as an important guide in determining the adequacy of digitalization and in the recognition and management of digitalis toxicity in children and infants (Giardina *et al.*, 1975).[15]

1.6 Genetic factors

Although genetically determined differences in hepatic enzyme activity are probably responsible for much of the observed variation in drug response (Vesell, 1974), direct evidence is only available for a few substances. In the field of cardiac drugs, it is known that the rate of acetylation of procainamide is under genetic control, and the general population may be divided into slow and fast acetylators (Dreyfuss *et al.*, 1972; Gibson *et al.*, 1975; Karlsson *et al.*, 1975; Karlsson and Molin, 1975; Reidenberg *et al.*, 1975). It appears likely that the production of the lupus-like hypersensitivity reaction associated with procainamide treatment is found mainly in fast acetylators, and this suggests that *N*-acetyl procainamide may be the agent responsible for this unwanted effect (Davies *et al.*, 1975). More recently, it has been shown that slow acetylators are more susceptible to the lupus-like reaction (Larsson *et al.*, 1977; Woosley *et al.*, 1978) against the hypothesis that the acetyl derivative is responsible. Zacest and Koch-Weser (1972) have suggested that the metabolism of propranolol may be under genetic control, the population being divisible into rapid and slow metabolisers, but this suggestion awaits confirmation.

1.7 Patient compliance

Failure of patients to take the medication provided for them is a major cause of apparant lack of response to treatment (Åberg, 1977). Weintraub *et al.* (1973), in a study of patient compliance as a determinant of serum digoxin concentration, found that the percentage of compliant patients fell from 82 to 60% when a second drug such as a diuretic agent was added to the treatment regimen. Compliant patients had a mean serum digoxin concentration of 1.2 ± 0.8 ng ml^{-1} ($\pm$ SD), whereas that of the non-compliant patients was 0.7 ± 0.7 ng ml^{-1}. When little therapeutic response is seen to a drug, therefore, particularly in out-patients, estimation of a drug's blood or urine level may be a useful first approach to assess patient compliance. Measurement of steady-state plasma propranolol levels has recently been recommended under such circumstances (Briggs *et al.*, 1975). Intensive supervision with a check on doses taken may improve out-patient compliance (Macdonald *et al.*, 1977).

1.8 Disease states

Marked differences in the kinetics of lignocaine have been found in patients with congestive cardiac failure when compared to normal subjects (Thomson *et al.*, 1969; Halkin *et al.*, 1975), and could be due to changes in volume of distribution of the drug, or to haemodynamic changes in the liver and kidneys. Patients with acute myocardial infarction exhibited abnormal kinetics of aprindine (Hagemeijer, 1975) and lignocaine (Aps *et al.*, 1976). Quinidine pharmacokinetics are also altered in patients with congestive heart failure (Crouthamel, 1975). In this last study, decreased perfusion of body tissues was suggested as a likely cause of the decreased volume of distribution leading to higher serum concentrations of quinidine in such patients.

Gastro-intestinal disease may influence drug absorption. In coeliac disease, absorption of practolol (an example of a water-soluble beta-blocker) is delayed, although plasma propranolol levels were higher in coeliac patients than in normal volunteers (Parsons and Kaye, 1974). These findings are consistent with the physicochemical nature of the drugs and with the pathology of the condition.

The influence of liver and renal disease on drug kinetics has already been discussed.

Changes in *thyroid status* may influence metabolism and excretion of drugs. It has been shown that the serum digoxin levels of hyperthyroid patients are significantly lower than those of hypothyroid patients (Doherty and Perkins, 1966), and this seems likely to be due in part to the significantly lower glomerular filtration rates found in hypothyroid patients compared with hyperthyroid patients (Croxson and Ibbertson, 1975) (Section 4.10.4). This effect might also be relevant when other drugs, which are mainly eliminated via the renal route (such as procainamide and practolol), are being administered to patients with thyroid disease. It is well known that the rate of metabolism tends to be higher in hyperthyroid patients than in the normal, and the reverse in hypothyroidism (Vesell *et al.*, 1975). Those drugs with clearance limited mainly by metabolism in the liver (such as digitoxin, lignocaine, quinidine) may, therefore, require a modified dosage in such patients (Bell *et al.*, 1977), whereas for propanolol, where the limiting factor is hepatic blood flow, there is little effect. The measurement of drug levels would aid the physician in deciding the optimum dose and frequency of administration in patients with altered thyroid function.

1.9 Drug interactions

Drug interactions should always be borne in mind as a source of variation

in response to treatment, since both in- and out-patients commonly receive several drugs concurrently (Smith *et al.*, 1966; Brater and Morelli, 1977). One drug may alter the amount of another available to the body, whether the interaction be in an infusion bottle, a syringe or in the gut. If a drug is highly protein-bound, another may reduce this binding, and even though the change may be small, this could lead to a marked increase in the circulating free drug concentration. In such circumstances, measurement of free, rather than total drug concentration, although technically more difficult, would be appropriate. The response of the heart to a particular drug may be altered by the presence of another, and this effect may sometimes be of therapeutic value, for example propranolol and quinidine may be used in combination in the treatment and prevention of cardiac arrhythmias, since by using smaller doses of each, untoward effects may be less than the sum of the effects of each drug alone (Stern, 1971), and combined use of propranolol and digoxin may be useful in angina pectoris (Crawford *et al.*, 1975).

Drug interactions concerned with hepatic elimination are dealt with elsewhere in this chapter. Interactions between drugs can also occur in the renal tubule, but these are of clinical importance only in those drugs which are mainly eliminated unchanged by this route, or where the metabolite of the drug is pharmacologically active and is eliminated by the kidneys.

Except where the possible interaction involves a readily measurable response, possible drug interactions can often be recognized by the measurement of steady-state circulating free drug concentrations. However, despite the fact that so many patients receive several drugs, adverse interactions are not common. One reason for toleration of these drug combinations may be the relatively flat dose response curves that most drugs possess (Azarnoff, 1974). The cardiovascular interactions of importance have recently been reviewed by Hutcheon (1975) and Koch-Weser (1975a).

1.10 Indications for estimation of blood levels of cardiac drugs in routine clinical practice

(*a*) To assess the bioavailability of a drug from a particular formulation. As has been pointed out earlier in this chapter, the amount of drug made available to the body from a certain formulation depends upon many factors, both in the drug itself and in the other constituents. While it is desirable to have evidence of availability for any new formulation, it is particularly important for poorly soluble drugs such as the digitalis glycosides.

(*b*) To establish that a therapeutic level has been achieved in the following circumstances:

(1) Where the drug has a low therapeutic ratio, the dose required to produce a therapeutic effect being close to that producing toxicity. This applies to many cardiac drugs, including the digitalis glycosides, lignocaine and quinidine (Rawlins *et al.*, 1977).

(2) Where the drug has 'awkward' kinetics, in order to assist in determining the dose required and its frequency of administration. Important examples are procainamide with its relatively short half-life of elimination, particularly in fast acetylators, and lignocaine with its varying volume of distribution in patients with cardiac failure.

(3) Where the patient may have particular problems in handling the drug, for example, in the very young or elderly patient, or in the presence of renal disease or hepatic disease or enzyme inducers.

(*c*) To differentiate sub-therapeutic from toxic doses when the clinical picture is confusing. It may be difficult, for example, to determine if a patient with severe cardiac insufficiency and arrhythmias is having too little or too much digitalis,* and a serum level may provide an answer.

(*d*) To assess patient compliance, when failure to respond to medication, particularly in an out-patient, raises the question of a patient's co-operation in treatment.

Thus, the measurement of drug levels in biological fluids can provide useful information to the physician enabling optimal therapy to be prescribed for each type of patient. Such measurement would be a helpful supplement to clinical judgement (Atkinson, 1973) and the usefulness of drug concentrations as therapeutic guides is now well-documented (Koch-Weser, 1972, 1975b; Prescott, 1972; Hayes, 1974; Werner *et al.*, 1975).

Addenda

(1) Use of drug level monitoring – plasma levels or serum levels are far more meaningful for controlling or deciding upon optimum therapy than simply using the dose level as a guide (Walther *et al*, 1978).

(2) Plasma digoxin levels are relevant and useful as a guide for therapy (Biddle *et al.*, 1978).

(3) There is a significant correlation between plasma and papillary muscle digoxin concentrations in patients (Lichey *et al.*, 1978).

* The term 'digitalis' is used throughout this book as a short term to cover all the digitalis glycosides and not to refer specifically to the powdered leaf of *Digitalis purpurea*.