Inter-Individual Differences in Response to Cardiovascular Drug Therapy

C.F. GEORGE BSc, MD, FRCP
V.F. CHALLONER MB, MRCP
D.G. Waller BSc, DM, MRCP

Clinical Pharmacology Group
Medical & Biological Science Building
Bassett Crescent East
Southampton S09 3TU, UK

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Summary:

1. When prescribing for patients with cardiac disease, it is important to attempt to identify any peculiarities which may lead to an abnormal response to treatment. If none are obvious the conventional dose can be administered.
2. If the patient fails to derive benefit, possible causes include misdiagnosis, a failure of the patient to take the medicine in the manner in which it was prescribed, an inadequate dose due to poor bioavailability or rapid elimination and true (pharmacodynamic) resistance to therapy.
3. Alternatively, if the patient complains of new symptoms within a few days of commencing therapy, these may reflect deficient inactivating systems or an abnormal sensitivity to a therapeutic concentration of the drug.
4. Careful dosage adjustment is, therefore, necessary to achieve optimum benefits from cardiovascular drug therapy.

Introduction

Drug treatment of cardiac disease can produce its beneficial effects through a variety of different mechanisms. Some drugs mimic or block with effects of endogenous substances such as the catecholamines by interacting with specific drug receptors. Others affect the activity of certain enzymes: for example, the antiplatelet agents, sulphinpyrazone, and aspirin, inhibit cyclooxygenase. Thirdly, there may be "nonspecific" actions on cellular function through effects on ionic fluxes across cell membranes, a property shared by many of the membrane stabilising agents used to treat arrhythmias. But, whatever the mechanism and locus of drug action, for the majority their magnitude of effect is related to the free concentration in extracellular fluid. This latter is in equilibrium with the concentration of drug which is free in plasma water. Good examples of these principles can be found for propranolol and other β-adrenoceptor blocking drugs. Thus, McDevitt et al[1] showed that the effects of propranolol were closely correlated with its free concentration in plasma. Furthermore, clinical correlations have been observed between dose and the extent of its effects in angina pectoris[2] and for plasma concentration and control of ventricular arrhythmias.[3] A further example of this phenomenon is shown for the first nine patients whom we recently studied in a trial to demonstrate the efficacy of nifedipine in patients whose angina pectoris was already being treated with a single daily dose of atenolol 100mg (Fig. 1).

Four main factors can be demonstrated to have an mportant bearing on the response of individual patients to medicines prescribed for them. These are compliance, pharmaceutical formulation, pharmacokinetic differences and pharmacodynamic variability.

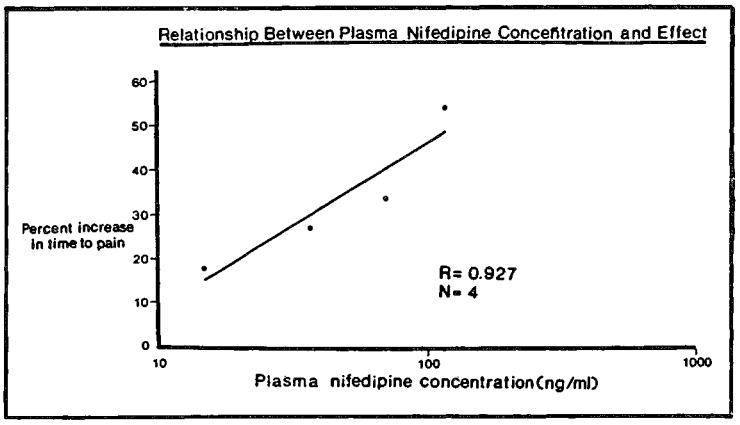

Fig 1
Relationship between plasma nifedipine concentrations and time to pain in nine patients with angina pectoris. All patients were already stabilised on atenolol 100mg daily (Challenor, Waller and George – unpublished data).

Compliance

It is frequently assumed that once a prescription has been issued for a patient he/she will automatically comply with the doctor's instructions. There is, however, evidence that some prescriptions are not taken to the pharmacist for dispensing and that a larger proportion of those who actually collect their medicines do not take them in the manner which was intended. This phenomenon has been extensively studied: see Sackett and Haynes.[4] For example, less than 50% of out-patients take their antihypertensive therapy in the intended manner. Various strategies have been employed to try to improve upon this, including simplifying the dosage regimen, for example, to once daily (see below) and involving the patient in monitoring his own response to therapy. In some drug trials, patients who do not comply have been specifically excluded from participating: for example, in the Veterans Administration studies on antihypertensive medication.[5,6] However, the demonstration of the marker substance, riboflavin, in urine does not necessarily infer that the patient is fully complaint. For example, some patients will be prepared to take a fixed number of tablets each day eg. one tds, but will not increase the dose further. Patients such as the one shown in Figure 2 would have a marker substance in their urine, but only plasma concentration data would reveal whether or not an increase in the latter had occurred with an increment in dosage.

Pharmaceutical Variation

In order for a tablet to produce benefit, it must first disintegrate within the gastrointestinal tract and then dissolve. The extent and rapidity with which these processes occur will depend upon the manufacturer's formulation. The manufacturer may, for example, specifically attempt to delay the absorption of a drug by formulating it as a slow release preparation. Such preparations have the advantages of reducing the height of the peak plasma concentration (and, therefore, reducing some side-effects) while prolonging the half-life of the drug, if the latter is short. Thus, a change from a conventional formulation to a slow release one may reduce the incidence of side-effects, and improve compliance because of this and the reduced number of doses which have to be taken each day. However, pharmacokinetic characteristics of the drug may be influenced by other factors including whether or not it is taken concurrently with food (see below).

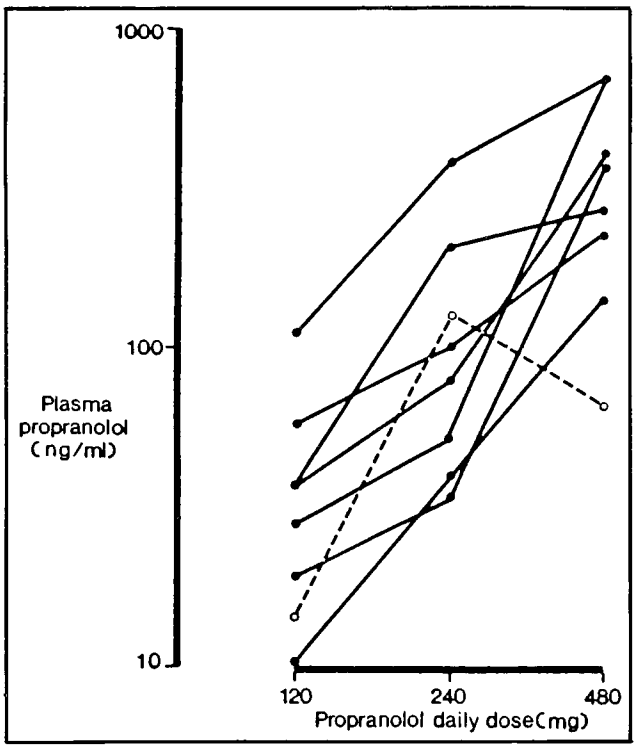

Fig 2
Relationship between daily intake of propranolol and plasma concentration achieved in nine patients participating in a clinical trial of propranolol and bufuralol in hypertension. The patient identified by the hatched lines failed to increase his dosage and his failure to comply completely, was confirmed by a tablet count.

Pharmacokinetic Variation

From the introductory remarks it should be clear that the effects of a drug relate to its absorption, distribution, metabolism and elimination characteristics. The most important factors affecting its actions are the dose, the proportion of this which reaches the systemic circulation unchanged (bioavailability), its distribution volume in the body, protein binding and the rate of elimination.[7] However, the pharmacokinetics of an individual drug can be subject to both genetic and environmental influences. Genetic differences among patients have been clearly demonstrated for a variety of metabolic reactions. In general, two types of reactions occur, mostly within the liver. The first type known as phase 1 or preconjugation reactions, take place in the mixed function oxidase system located within the smooth endoplasmic reticulum. Oxidation, reduction or hydrolysis occurs to reveal a reactive chemical grouping on which a subsequent synthetic reaction can occur. This second phase (phase II) reaction is a conjugative or synthetic one in which an additional chemical group such as an N-acetyl or glucuronic acid is attached. Both types of reactions lead to a reduction in the lipid solubility of the parent molecule and the products are, therefore, easier to eliminate from the body, usually in the urine (but sometimes in bile).

In recent years genetic polymorphism of the mixed function oxidases has been demonstrated.[8,9] One substrate which has been extensively studied is debrisoquine, an adrenergic neurone blocking drug. When given to people who are genetically poor hydroxylators it produces excessive hypotension. Since this description, a number of other substrates have been shown to utilise the same enzyme: among these are metoprolol and bufuralol. For metoprolol an increased

pharmacologic effect (bradycardia) can occur due to the higher plasma concentrations found in deficient hydroxylators. But with bufuralol, another experimental β-adrenoceptor antagonist, nausea and vomiting occur in deficient hydroxylators.[10] Polymorphic drug oxidation is claimed also for nifedipine[11] but the enzyme responsible for its metabolism is different to that which biotransforms metoprolol and debrisoquine.

N-Acetyltransferase, a conjugative enzyme, also displays genetic polymorphism. In the United Kingdom approximately 50% of the population are fast metabolishers of this drug.[12] Fast metabolishers tend to have a lesser response in terms of blood pressure reduction but are also less prone to develop the SLE syndrome at conventional therapeutic doses, than are slow acetylators (but who develop a greater therapeutic response).

Environmental factors which alter the pharmacokinetics of various cardiovascular-acting drugs include food, smoking habits, concurrent drug therapy and disease states.[14] Ageing is another factor which may lead to alterations in drug pharmacokinetics.[15]

The effects of food on drug pharmacokinetics have been reviewed by Melander and McLean[16] and by George.[17] Recent studies from our group have shown that food can have considerable effects on the pharmacokinetics of various formulations of nifedipine.[18,19] Current advice is that capsule formulations should be taken with food. When this advice is heeded the peak plasma concentrations are reduced and the half life is prolonged, giving the product "slow release" characteristics. Obviously, these effects will not obtain if the patient disobeys the instructions, in which case high peak concentrations may occur and create side-effects: in addition the duration of effect will be reduced. By contrast, when biphasic capsules (quick-slow) are used, their co-administration with food appears to delay the passage from the stomach into the duodenum and destroys the slow release characteristics of this formulation.

Smoking has been shown to induce some mixed function oxidases in the liver. In particular, cytochrome P_{448} activity is increased and this leads to a change in the clearance of certain drugs whose half-lives may be shortened and bioavailability reduced.[20,21] For propranolol and theophylline this may lead to a reduction in their pharmacological and therapeutic effects. Other drugs can increase the activity of microsomal mixed function oxidases. Notable amongst these are hypnotic agents, including barbiturates, dichloralphenazone and many anticonvulsants, e.g. phenytoin and carbamazepine. Griseofulvin shares this property and like the others can increase the metabolic degradation of compounds like warfarin to necessitate an increased dosage for anticoagulant control.

By contrast, other drugs including cimetidine and allopurinol can inhibit drug oxidation within the liver to increase the pharmacological effects of other agents and prolong their effects. For example, we[22] have recently demonstrated an increased bioavailability of nifedipine during treatment with cimetidine (but not ranitidine).

Disease states may modify the pharmacokinetics of drugs in a variety of ways. In theory, disease of the gastrointestinal tract may reduce the absorption of a drug but in practise this does not usually occur except in the presence of gastroenteritis or paralytic ileus. Reduced splanchic blood flow of a result of heart failure may occasionally lead to impaired drug absorption.[23] Reduced protein binding of drugs occurs in patients with low serum albumin concentrations as a result of either liver disease or the nephrotic syndrome.[24] The reduced binding leads to an increased pharmacologic effect, to a change in distribution and to altered elimination rate. By contrast, propranolol and lignocaine, which bind to α_1-acid glycoprotein show a diminished distribution volume where acute inflammation occurs as following an acute myocardial infarction.[25]

For other drugs elimination depends upon glomerular filtration and, therefore, upon cardiac output. The elimination of these agents will, therefore, be reduced in patients with heart failure and others with renal disease (or ageing).[26,27] Thus, the administration of "normal" sized doses to patients with either cardiac disease of myxoedema (and a low cardiac output) may lead to arrhythmias with digoxin, bradycardia with atenolol or sotalol, hyperkalaemia with amiloride and anticholinergic effects (including urinary retention) with dispyramide. However, for the majority of drugs the rate of elimination is determined by metabolism in the liver. Disease of this organ may, therefore, lead to a prolongation of a drug's action due to a reduced clearance from the blood. By contrast, when the drug is orally administered its bioavailability may be enhanced, as a result not only of reduced presystemic metabolism but also because of a bypassing of the liver through porto-systemic anastamoses. The magnitude of these changes varies according to the drug being used and the extent of liver disease.[28] It is most likely to be important in patients who have evidence of decompensation, e.g. encephalopathy, jaundice and ascites.[29]

In addition to the effects of disease itself the treatment, which may be necessary, can have important effects. For example, the antiplatelet agent sulphinpyrazone has an active metabolite, sulphinpyrazone sulphide. This product is more potent than the parent drug and has a longer duration of action.[30] This active metabolite is formed from the parent drug by reduction within the microbial flora of the gastrointestinal tract.[31] This reaction cannot take place unless there is an intact colon and is lacking in those patients who have had an ileostomy fashioned for inflammatory bowel disease.[32] Concurrent antibiotic therapy can also reduce the formation of this active metabolite.[33]

Pharmacodynamic variability

Studies on pharmacodynamic differences between individuals are relatively few in number. There are however, a small number of examples in which genetic factors have been implicated, for example, congenital resistance to warfarin. In addition, the development of the SLE syndrome in patients treated with hydralazine is more likely to occur in patients with a particular HLA status.[34] Further examples include individual differences in the sensitivity of β-adrenoceptors,[35,36] a parameter which appears to decline with increasing age.[37,38] These pharmacodynamic differences have been emphasised in my recent paper given in Singapore[39] and further examples can be found in the book by Smith and Rawlins.[40]

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