Dose-response relationships in clinical pharmacology.
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DOSE RESPONSE RELATIONSHIPS IN NORMAL VERSUS DISEASED SUBJECTS

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INTRODUCTION

Most early studies of drugs in man are carried out in healthy volunteers. Thus, once animal pharmacological studies have been completed the earliest pharmacokinetic and pharmacodynamic studies are usually undertaken in individuals without the disease for which the drug in question will eventually be used. While knowledge of the normal pharmacology of the drug is certainly of value, the temptation in the past has been to pay too little attention to the diseased state and to assume that the effects of the drug will be similar in patients to that seen in healthy volunteers. Although few major problems have come to light it is clear that there are both qualitative and quantitative differences between the two. In the first case the pharmacokinetics of the drug may be altered by the disease process and this aspect of the subject has received considerable attention over the last few years. Secondly, however the changes produced by the disease process may be pharmacodynamic rather than pharmacokinetic and this aspect of the dose-response relationship has received relatively little attention.

PHARMACOKINETICS IN DISEASE

Pharmacokinetics includes the absorption, distribution, metabolism and elimination of drugs, although as far as disease is concerned it is the latter two subject areas that have received the most attention.

Absorption of drugs in Disease

Most drugs are absorbed by passive diffusion and the reserve capacity in the intestine makes it very unlikely that a disease process will affect drug absorption significantly. A disease that slows gastric emptying (eg gastric ulcer, pyloric stenosis) may reduce the rate at which a drug is absorbed but it is unlikely to affect the total amount of drug absorbed (1). In patients with coeliac disease the absorption of some drugs such as amoxycillin is impaired but in contrast the absorption of propranolol is enhanced in patients with coeliac disease (2). The absorption of ethinyloestradiol is also increased in patients with coeliac disease and here the mechanism is now elucidated (3). Ethinyloestradiol has an average bioavailability in man of 45% and this reduced bioavailability is due to first pass metabolism of the drug in the gut wall

(4). Ethinyloestradiol is extensively conjugated with sulphate by the jejunal and ileal mucosa and in coeliac disease this conjugation mechanism is deficient, which as a result leads to increased bioavailability. A gluten free diet restores sulphate conjugation to more normal levels and as a result bioavailability is again reduced (3).

Distribution of drugs in disease processes

Once a drug is absorbed it is distributed to its sites of action via the blood stream. Many drugs are bound to plasma proteins and it is only free drug that is pharmacologically active. Most drug assays only measure total drug concentrations in plasma on the assumption that the free concentration will always be a fixed proportion of this total. This may be correct for normal individuals but a number of diseases may perturb the relationship. Acidic drugs in general bind to serum albumin and diseases that produce hypoalbuminaemia may reduce the binding of drugs thus increasing free concentrations (5). This is particularly true in the nephrotic syndrome where it has been calculated that for each 1 $g.l^{-1}$ fall in serum albumin there is a 1% decrease in the percentage of phenytoin bound to proteins (6). In some disease states it is not the absolute amount of albumin that is decreased but the affinity of the albumin to bind drugs. This is best known in uraemia where the binding of many acidic drugs is markedly reduced. It is perhaps most important for phenytoin since therapeutic drug monitoring using total drug concentrations is widely employed. Although the normal therapeutic range is 10-20 $mg.l^{-1}$, for a patient with uraemia, the same free concentration may be obtained at total concentrations 2.5-5 $mg.l^{-1}$ (7).

Basic drugs are bound in plasma to acid $alpha_1$ glycoprotein (AAGP) and a number of disease processes may increase concentrations of AAGP and thus increase the binding of basic drugs (8). Most inflammatory conditions such as infections will raise the level of AAGP which is one of the acute phase proteins and AAGP levels are also increased in patients following trauma, surgery, burns and myocardial infarction. The implications of this are best exemplified by lignocaine. In normal subjects the free fraction of lignocaine varies from 20 to 40% but in diseases that increase the AAGP concentration in blood, the free fraction of lignocaine falls to less than 20% (9). Thus patients with heart failure, or myocardial infarct appear to tolerate well concentrations of lignocaine that would usually be associated with toxicity.

In heart failure the kinetics of drugs like lignocaine are affected in other ways. The volume of distribution of lignocaine is reduced and its metabolism is impaired both in patients with heart failure (10) and in patients with myocardial infarction (11). These changes are due both to a reduced hepatic

blood flow and to an impaired ability of the hepatic drug metabolising enzymes. Theophylline kinetics are also affected in heart failure due to an impairment of drug metabolism (12). Impaired theophylline metabolism is especially likely in severe heart failure and toxic side effects may ensue.

Drug metabolism in disease

Numerous studies have been done to look at the effect of various disease processes on the metabolism of drugs. The most obvious diseased organ is the liver since most modern drugs are extensively metabolised in the liver. The liver has a considerable capacity to metabolise drugs and significant changes are only seen when the liver is severely damaged (13). In general both phase 1 and phase 2 processes may be impaired in severe liver disease. In cirrhosis there is usually a defect not only of liver function but also of hepatic circulation. This will affect both high clearance drugs and low clearance drugs. Drugs with the highest hepatic clearance will have the largest relative increase in bioavailability in cirrhosis (14). The clinical implications will depend on the nature of the drug. In most cases enhanced efficacy or toxicity will ensue but in some instances where the activity of the drug depends on metabolism to an active metabolite, the efficacy of the drug may be decreased. The metabolism of drugs may also be impaired in other disease states (15). Thus in febrile states, renal failure, diabetes mellitus, respiratory disease and thyroid disease the metabolism of drugs may be impaired. The situation in thyroid disease is of particular interest and will be discussed later in the chapter. In general, drug metabolism is enhanced in hyperthyroidism and impaired in patients with hypothyroidism with a return to control values when the disease process is corrected (16).

Drug elimination in disease

Drugs which are largely cleared by renal excretion show a prolonged half life in patients with impaired renal function. Thus the half life of drugs like digoxin, and the aminoglycoside antibiotics is prolonged in such patients. Patients with impaired renal function will need lower maintenance doses of digoxin (or less frequent dosing) but the initial loading dose will not be affected by the disease process (17). It is often assumed that it is only drugs that are excreted unchanged by the kidney that will accumulate in plasma in patients with renal failure. This is however not necessarily true. The active metabolite of procainamide, N-acetyl procainamide is eliminated less efficiently in patients with uraemia than the unchanged drug (18). This leads to accumulation of N-acetyl procainamide in the plasma and adverse effects have been noted. Accumulation of toxic metabolites in patients with renal failure have been shown for other drugs such as allopurinol, clofibrate, methyldopa,

pethidine and sulphonamides (18). The kinetics of drugs may be altered in other ways in patients with impaired renal function and we have seen how protein binding of drugs can be affected (7). Diazoxide, like phenytoin is bound to albumin and in renal failure, free concentrations of diazoxide increase in plasma. It has been clearly shown that diazoxide is more effective in patients with impaired renal function and the enhanced fall in blood pressure correlates well with the increased free concentrations of diazoxide (19).

Drug kinetics in other diseases

Although much attention has been paid to the effects of liver, renal and heart disease on the kinetics of drugs, little attention has been paid to the effects that a disease may have on the kinetics of a drug given for the treatment of that disease. It has always been assumed for example that the kinetics of non-steroidal anti-inflammatory drugs (NSAIDs) are similar in patients with rheumatoid arthritis to that seen in age matched controls. However recent studies have shown that this is not the case (20). Six patients with active rheumatoid arthritis were given naproxen and the kinetics was contrasted to that seen in the same patients a few months later when the disease was much improved. In the active disease phase total naproxen concentrations were significantly lower while the unbound concentration was higher. This was associated with a higher volume of distribution and a lower total albumin concentration in the active disease phase.

In malaria the pharmacokinetics of many drugs are currently being examined and again the blood levels in disease are different to that seen in normal volunteers. Quinine, widely used nowadays for the treatment of Plasmodium falciparum infections, has been examined by White and his colleagues in Thailand (21). In patients with cerebral malaria the clearance of quinine (given i.v.) is reduced and the volume of distribution is also reduced. This leads to higher total concentrations of quinine, and in these patients concentrations of quinine often exceed 15 $mg.l^{-1}$. Severe side effects of quinine, such as blindness and cardiac arrhythmias are rare in these patients whereas similar concentrations in individuals who have taken an overdose of quinine often cause such effects (22). The explanation for this may lie in part in increased binding of quinine to AAGP since free concentrations of quinine are certainly reduced in patients with cerebral malaria (23).

The kinetics of chloroquine, another drug used to treat malaria are altered in such patients. Chloroquine has a very large volume of distribution and part of the explanation for this is binding to white cells and red cells in blood. However in patients with malaria the red blood cell to plasma ratio for chloroquine is increased. The ratio is 25:1 at the start of treatment and

declines to the more normal ratio of 5:1 as the parasite levels in the blood fall (24). Amodiaquine is a structurally similar antimalarial drug to chloroquine, although its kinetics are quite different. It acts almost like a prodrug and its main metabolite, desethyl amodiaquine is the source of most of the antimalarial effects. Although amodiaquine does not accumulate in red cells, desethylamodiaquine does with a red cell to plasma ratio of about 3:1 (25). Recent studies in patients with malaria have shown that when parasite levels are high, desethylamodiaquine does not enter red cells and as parasite levels fall the ratio of red cell to plasma concentrations of this metabolite rise. The exact relevance of these findings is unclear but they may help to explain the mechanism of action of these antimalarial drugs, particularly in drug-resistant disease.

PHARMACODYNAMICS OF DISEASE

Dose response in liver disease

We have already seen that the kinetics of many drugs are altered in liver disease, the natural assumption is to ascribe the cause to altered kinetics. Studies with morphine many years ago showed that patients with cirrhosis of the liver showed markedly enhanced EEG effects when given small (8mg) doses when compared to normal controls (26). Although plasma morphine concentrations were not available at that time, subsequent studies have shown that morphine kinetics are not impaired in patients with cirrhosis (27). Similar studies with chlorpromazine have shown markedly enhanced EEG and sedative effects of chlorpromazine in patients with compensated cirrhosis compared to control patients (28). However as with morphine the kinetics of chlorpromazine in these patients was not altered compared to controls and the enhanced CNS effects must be due to increased sensitivity of the cerebral neurones.

Dose response in renal disease

In patients with renal functional impairment, drugs like gentamicin and digoxin which are excreted unchanged by the kidney would be expected to produce more toxic effects than in patients with normal renal function. However differences in drug responses may be seen with drugs that are only excreted as metabolites. Morphine may have enhanced effects in patients with renal disease (29) and this is thought to be due to accumulation of the metabolite morphine-6-glucuronide (30) one of the rare situations of a conjugated metabolite which is pharmacologically active. Although altered pharmacokinetics also explains the great majority of such examples in renal disease, Galeazzi et al (1979) (31) found that the beta adrenoceptor blocking drug pindolol produced greater inhibition of exercise induced tachycardia in patients with uraemia than in

control patients in spite of very similar blood concentrations of the drug. The increased hypotensive effect of diazoxide in patients with renal failure, referred to earlier, has a kinetic explanation due to the increased free concentrations of the drug (19).

Dose response in thyroid disease

It has long been recognised that the presence of thyroid disease may alter the response to a particular drug. Thus, for example, patients with hypothyroidism are particularly sensitive to digoxin, while those with hyperthyroidism need larger doses to produce clinical benefit or toxic effects (32). Digoxin is a drug that is almost exclusively eliminated unchanged by the kidney so changes in kinetics are unlikely to be the explanation here. However drugs that are metabolised by the liver also have their clinical responses altered by thyroid disease and here alteration in kinetics may play a role. In patients with hyperthyroidism, gastrointestinal motility, liver blood flow, and renal blood flow are increased and albumin levels and AAGP levels are decreased with opposite effects seen in patients with hypothyroidism (33). All these factors affect drug kinetics. In addition, in patients with hyperthyroidism the rate of drug metabolism is usually increased, with an average of 40% decrease in the antipyrine half life (33,34). Thus the dose of propranolol required to achieve therapeutic concentrations of the drug in patients with hyperthyroidism is usually greater than seen in euthyroid patients (35). In patients with hypothyroidism the reverse is usually seen with an impairment of drug metabolism and an increase in antipyrine half life of up to 100% (33,34). However these kinetic changes, and indeed the other documented effects on kinetics in thyroid disease do not explain all the altered responses to drugs. Thus Scott et al (36) showed no overall change in the kinetics of oxazepam in patients with hypothyroidism compared to controls and yet the sedative effects of oxazepam were markedly greater in the patients with hypothyroidism. This must suggest an altered receptor sensitivity. There has been considerable debate over the issue of receptor sensitivity or receptor numbers in thyroid disease. In early studies no evidence for altered receptor sensitivity could be found. The known increased sensitivity to catecholamines in patients with hyperthyroidism was thought not to be due to receptor changes since adenyl cyclase responsiveness did not change (37). However subsequent studies suggest that in hyperthyroidism there is an up-regulation of the beta adrenoreceptors in the heart (38), primarily due to an increase in membrane-bound receptors, and that there is also a marked decrease in alpha receptor numbers (39). The exact relevance of these observations needs clarification but it is clear that altered dose response relationships in thyroid disease are due to both kinetic and dynamic causes.

Dose response in heart failure

We have already noted that the pharmacokinetics of many drugs are altered in heart failure primarily by a change in the volume of distribution or a reduction in the rate of metabolism. However these changes do not necessarily explain the altered response to drugs. The response to digoxin for example is dependent upon a number of factors listed in table 1.

TABLE I

FACTORS AFFECTING THE MYOCARDIAL SENSITIVITY TO A GIVEN PLASMA DIGOXIN CONCENTRATION

Increased sensitivity	Reduced sensitivity
Hypokalaemia	Hypocalcaemia
Hypercalcaemia	Hyperkalaemia
Hypothyroidism	Hyperthyroidism
Hypoxia	
Old age	
? Hypomagnesaemia	

After Aronson 1980 (40)

Most of these factors, except perhaps old age do not affect the pharmacokinetics of digoxin.

The pharmacokinetics of theophylline are also perturbed in heart failure (12,41) with reduced total body clearance of theophylline in cor pulmonale which has led writers to suggest that the dose of theophylline should be reduced in heart failure (41). However, is this advice justified since we have no evidence that the normal plasma concentration:response relationship is true in patients with heart failure? There has been a considerable amount of work on the pharmacodynamic aspects of heart failure and on receptor sensitivity and receptor numbers. Heart failure is characterised by hyperactivity of sympathetic pathways and circulating catecholamine concentrations are raised (42). In the failing heart there is a decrease in catecholamine sensitivity due to reduction in the beta adrenoceptor number ('down' regulation) (43). In further work this down regulation of beta adrenoceptors in the failing human heart primarily affects the β_1 receptor with a relative increase in the β_2 receptors (44). The down regulation of β_1 receptors is chamber specific - that is only affecting the ventricle that is failing. There does not appear to be any effect on myocardial α_1 adrenoceptors or histamine H_2 receptors (45). The apparent tolerance to the β adrenergic agonist pirbuterol in the long term treatment of patients with heart failure correlates with a decrease in beta adrenoceptor numbers on lymphocytes (46). It is thus clear that both dynamics and kinetics of drugs are altered in heart failure and it may be that the reduced receptor number is a consequence of elevated concentrations of beta

stimulants, both natural and synthetic.

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Discussion - Dose-response relationships in normal vs diseased subjects

W.S. Nimmo

You have mentioned that patients with cirrhosis of the liver show markedly enhanced EEG effects when given small doses of morphine, although glucuronidation of this drug is not impaired in these patients. Do you think that this increased effect could be explained by an alteration in the pharmacokinetics of the metabolite?

M. Orme

Morphine 6 glucuronide has been examined in patients with liver disease and slightly higher concentrations than those observed in normal subjects have been detected, but it doesn't seem to me that this actually explains all the difference. I think you get closer to the answer if you look at the metabolites, but they do not account for all the difference.

D.S. Davies

A possibility to be considered is that penetration of morphine or its active metabolite across the blood brain barrier may be altered in severe cirrhosis, so that there may be a kinetic explanation, but unrelated to elimination.

M. Orme

Yes, that is perfectly possible, but we have very poor data. On the other hand, even if data about concentrations in the CSF were available, I am not sure that they would necessarily correlate with what is happening in the brain.

H.J. McQuay

There is a lot of really quite good data showing that for many patients who have abnormal liver function the average morphine requirements are not different, so I think that explanations in terms of active metabolites may apply only to very severe cirrhotic disorders.

M. Orme

I would agree with that. It is important to remember that most studies have shown that changes in kinetics are only seen in patients with marked degrees of cirrhosis.

E. Perucca

I was interested in your data on changes in protein binding and the relationship between serum concentration and effect. Would you agree that in most situations the change that you get when you have an alteration in protein binding is in fact a change in the relationship between total serum concentration and effect, but not in the relationship between dosage and effect? In most cases, there are compensatory changes in clearance which bring back the serum concentration of free, pharmacologically active drug to the original level. The question really is whether you know of any situation in which a change in protein binding actually results in an alteration in the dose-response relationship. As far as uremia is concerned, it could be that what changes is not so much the pharmacokinetics, but the response, for example of the brain, to a given free drug concentration.

M. Orme

I would quite agree with you that the effect of the dose is relatively small. With drugs such as phenytoin, if people are not aware of the relationship they may actually go for a given serum concentration that is clearly toxic in patients with uremia. That is the risk. In fact, I am a firm believer that there really aren't any significant interactions in terms of protein binding, because you just get enhanced clearance, but perhaps that is an extreme viewpoint.

E.A. Carr

May I follow up your question? You talked about the effect of uremia and other abnormal conditions on the protein binding of a drug and therefore on the free concentration and on the drug's effect. Is there any evidence that binding to a receptor, not increase or decrease in the number of receptors but change in the affinity of a given drug for a given receptor, can be altered by disease?

M. Orme

There are some data, but not very good. A couple of studies have shown some changes in affinity but I think they are relatively minor.

B.P. du Souich

It seems to me that we often conclude that changes in kinetics are not responsible for a change in effect, essentially because we have been unable to correlate changes in plasma concentrations and effect. I am not sure that we are allowed to reach this conclusion because what counts is the concentration at the receptor site. Plasma concentrations do not necessarily reflect exactly what is going on at the receptor site.

M. Orme

I would obviously agree with that. We tend to measure total concentrations for a start and may later look at free drug in plasma or at concentrations in red cells, but there are many extrapolations to be made.