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The Effect of Disease on Drug Disposition

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Introduction

Clinical Pharmacology has been defined as the scientific study of drugs in man and it is in the setting of the disease state that this science must ultimately be applied Techniques for drug assay, tissue response elucidation and the determination of other important pharmacological variables have resulted in better understanding of the mechanisms of action of drugs and the way these agents are handled in the body.

This paper reviews the results of the application of these methods to study the effects of disease on drug disposition. This area of study is an important and ever expanding research interest of Clinical Pharmacologists and Clinical Pharmacists worldwide, The emphasis has been rightly placed since the information that is emerging not only improves prescribing practice but refines the art and science of drug use in therapeutics.

Pathological States

The pathological conditions considered in this review include:

1. Liver disease
2. Heart failure
3. Kidney failure and
4. Other disease stated affecting gastrointestinal motility.

Liver Disease

The liver is the main organ involved in drug metabolism. Liver disease should thus be expected to affect the way drugs are handled. It must also be noted that liver disease must be fairly extensive before abnormal drug metabolism occurs. Most of our patients are however seen with extensive liver disease because they present to hospital late. What are the effects of the liver pathology on the drugs we administer to them?

Liver disease does not impair the metabolism of all drugs to the same extent and it may be difficult to extrapolate from knowledge of the handling of one drug to another (1). This is because of the heterogeneity inherent in the different forms of Cytochrome P450 we possess.

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Some of these may are on different substrates and may be differently affected by hepatocellular dysfunction.

An example involves the hepatic hydroxylation of antipyrine and phenytoin. In cirrhosis, only the metabolism of antipyrine is affected.

Drugs may be classified into two main groups on the basis of their hepatic clearance – (a) high clearance and (b) low clearance characteristics. The ability of the liver to eliminate high clearance drugs after parenteral administration is dependent on the amount of blood flow to the liver.

Reduction in hepatic blood flow as may occur in heart failure will lead to reduced clearance of some drugs (Table 1). Low clearance drugs are dependent on the intrinsic Metabolizing ability of the liver and will be more affected by disease of the liver parenchyma. (2)

Table 1: Drug Clearance and Liver Disease (2)

Low clearance drugs	High clearance drugs
Diazepam	Lignocaine
Ampicillin	Labetalol
Penicillin	Propranolol
Prednisolone	Pethidine
Theophylline	Chlormethiazole

Protein binding

Plasma protein binding of drugs is altered in liver disease. The free fraction of the oral hypoglycaemic agent, tolbutamide is increased by as much as 115% in cirrhosis and that of phenytoin by up to 40%. These facts become important when we prescribe for patients with diabetes mellitus and seizure disorders. This also explains the increased incidence of adverse reactions associated with phenytoin in liver disease.

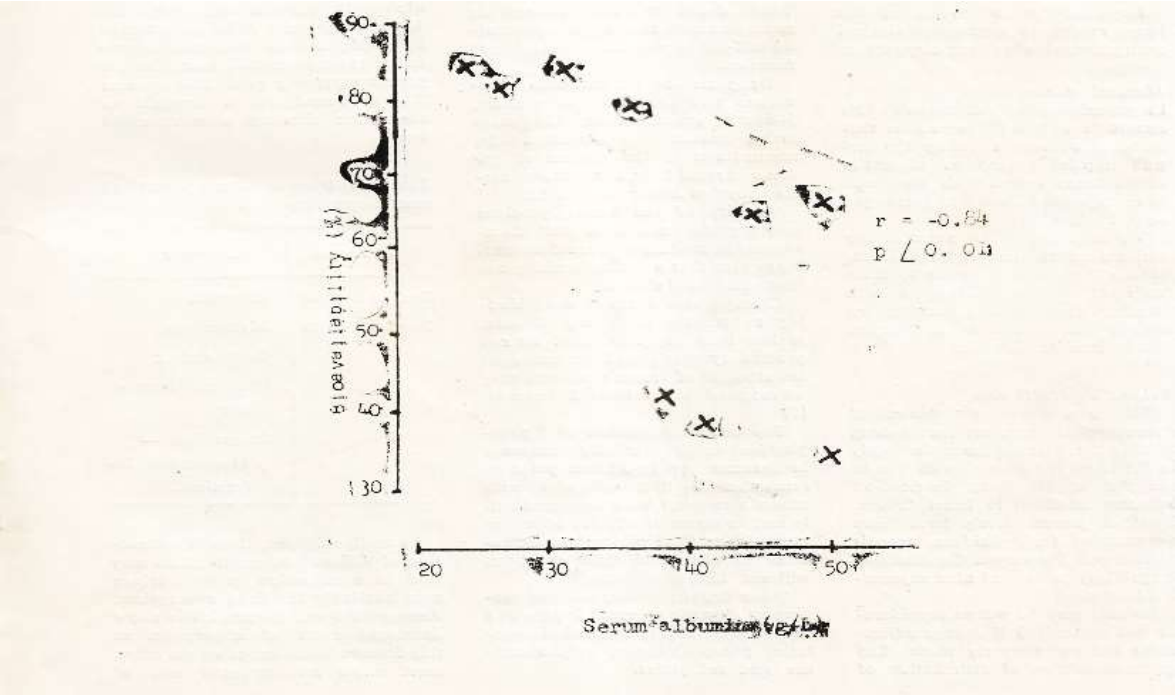
It has also been document that the dose of diazepam needed to produce sedation for endoscopy is less in cirrhotics that those with normal liver function. (3).

Portal hypertension

Portal hypertension occurs in liver disease. This results in oedema and structural abnormalities of the small intestinal mucosa. These changes are marred enough to alter drug disposition and absorption from the gut may be delayed.

Patients with hepatosplenic schistosomiasis show an increase incidence of central nervous system side effects from Niridazole. This has been attributed to elevated drug levels resulting from shunting of portal blood away from hepatic metabolism. This portocaval anastomosis that is established allows passage of orally administered drugs directly into the systemic circulation. This prevents hepatic first pass metabolism from reducing drug bioavailability. We have begun to see patients with S. Mansoni infestation in Ghana and Clinicians should remember these facts when dealing with such patients.

Figure 1



It has been difficult to establish a direct relationship between prothrombin time and drug clearance for all patients and this index may not be too helpful.

We should also be aware of the secondary effects of the liver disorder on other vital organs. The brain is extremely sensitive to centrally acting drugs in chronic liver disease. Coma is easily precipitated by non-therapeutic amounts of such drugs. (3).

It is only when Pharmacists and Clinicians are fully aware of the possibility of adverse drug effects from altered drug disposition in such disease states can a meaningful approach to therapy be adopted. Therapeutic drug monitoring and the use of agents eliminated via other routes offer management options in patients suffering from chronic liver disorders.

Cardiac Failure

Impaired 'pump' action of the heart results in pathophysiological changes which alter drug disposition.

Mucosal oedema

In prescribing for patients with this condition we should remember that mucosal oedema affecting the gut wall impairs absorption of orally administered drugs. This may lead to therapeutic failure and prolonged stay in hospital.

We have had to give some of our patients intermittent doses of intravenous frusemide in order to clear 'resistant' oedema. Diuretics with impaired absorption in heart failure include the thiazides, metolazone and hydrochlorothiazide.

Volume of distribution

This is a convenient theoretical concept which assumes that a drug is distributed throughout the body in the same concentration as it is the plasma. (4) Drug distribution becomes modified in heart failure. Elevated plasma levels have been documented for quinidine, procainamide and lignocaine. Cardio active drugs likely to be used after myocardial infarction.

Patients may be put at considerable risk of toxicity if dosage adjustments are not properly made. The apparent volume of distribution of the drugs are significantly reduced in heart failure. Drugs with a big volume of distribution have most of the drug load bound to the tissues. Drug elimination in heart failure is also reduced. This occurs because there is reduced blood flow to the kidney and liver.

The reduction in drug clearance by the kidney occur because glomerular filtration no longer occurs at the same rate during hear failure. This flow dependent elimination prolongs the half-life of procainamide for example.

Hypoxia impairing drugs oxidation or hepatocellular damage from hepatic congestion or hypo perfusion may be responsible for the reduced metabolic capacity of the liver in heart failure.

Kidney Disease

Many drugs are eliminated from the body via renal mechanisms. These drugs primarily cleared by renal excretion thus a prolonged half-life in patients with impaired function.

Drug metabolites can also accumulate and contribute to toxicity. N-acetyl procainamide, the main active metabolite of procainamide, accumulates in the plasma of patients in renal failure and causes cardiac rhythm abnormalities. (2)

Toxicity of the aminoglycosides and digoxin have been well documented in patients with renal disease. Steps aimed at avoiding toxicity are illustrated in table 2.

Changes also occur in drug binding to protein in kidney disease. It has been suggested that altered protein synthesis and structure of the albumin of uraemic patients may be responsible for these differences. (5)

The unbound fraction of diphenylhydantoin is markedly increased in uraemia. An important point to remember is that epileptics with uraemia respond both therapeutically and in terms of adverse effects at much lower total plasma concentration of phenytoin than epileptics without kidney disease.

Other drugs showing reduced binding to albumin in renal failure and hence increased toxicity include warfarin, phenylbutazone, sulphonamides and salicylates.

Drug administration in renal failure

1. Maintenance dose of the drug should be smaller and/or
2. The dose of the drug should be given less frequently
3. Review the fate and metabolism of the drugs administered
4. Examine patient often, nothing adverse drug effects.

Normograms have been drawn up as aids to appropriate drug schedule in renal failure. They may be helpful and should be used and appropriate revisions made for each individual patient.

Gastrointestinal Disease

Diseases altering the rate of gastric emptying affect drug absorption. Table 3. Delayed gastric emptying may produce therapeutic failure with aspirin in patients with migraine. More rapid pain relief is obtained by giving aspirin with metoclopramide. Metoclopramide increases the gastric emptying rate. This ensures that the analgesic is brought to absorption sites on a more rapid basis.

Table 2: Disease altering rate of gastric emptying

Increased	Decrease
Coeliac disease Duodenal ulcer	Migraine Myxoedema Gastric ulcer Intestinal obstruction Severe Pain-Myocardial Infarction

In coeliac disease, there is destruction of Villi and Microvilli. This may lead to a reduction in the surface area available for drug absorption. Amoxicillin and Pivampicillin show decreased rated of absorption in this disease. Some drugs on the other hand show an increased rate of absorption and include sulphamethoxazole, trimethoprim, clindamycin and fusidic acid.

Malabsorption stated are commonly encountered in tropical clinical practice and the research efforts of the Clinical Pharmacologist and Clinical Pharmacists should also be directed at drug responses in patients suffering from these conditions.

Iron deficiency anaemia is common disease entity amongst our patients. Changes in the stomach and intestines may be profound enough to alter drug absorption and individual responses. Third subject is being investigated presently at the Centre. (6).

Conclusion

While acknowledging that the effects of disease on drug disposition may sometimes be more academic than practical, it does not in any way lessen the importance of the subject under discussion.

Most preliminary drug studies are carried out on normal, healthy volunteers. The pharmacological patterns obtained in such studies may however differ markedly in those individuals suffering from disease.

It should be the duty of the Clinical Pharmacologist and Clinical Pharmacist to ensure that data is accumulated and analysed relating to the effects of disease on the pharmacokinetics of drugs. Nowhere is this more urgently needed than in the tropical milieu. We are presently importing drugs developed elsewhere without note being taken of the different pharmacogenetics,

pharmacokinetic and environmental factors which may be operating in this and other tropical countries.

The current scope of the research efforts of the Centre for Tropical Clinical Pharmacology and Therapeutics covers studies on the topic under discussion. The results emerging can only improve patient care.

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