cardiovascular and respiratory disease therapy

edited by

j. c. petrie

cardiovascular and respiratory disease therapy

edited by

J. C. PETRIE

1980
Elsevier/North-Holland Biomedical Press · Amsterdam · New York · Oxford

List of contributors

H. E. Barber – Senior Lecturer, Department of Pharmacology, University of Aberdeen, Medical Buildings, Foresterhill, Aberdeen AB9 2ZD, United Kingdom

Laurence H. Beck – Associate Chairman and Associate Professor of Medicine. Department of Medicine, University of Pennsylvania School of Medicine, 3400 Spruce Street, Philadelphia, PA 19104, U.S.A.

Leighton E. Cluff – Adjunct Professor of Medicine, University of Pennsylvania School of Medicine, Philadelphia. Vice-President, Robert Wood Johnson Foundation, Princeton, NJ 08540, U.S.A.

Colin T. Dollery – Professor, Department of Clinical Pharmacology, Royal Postgraduate Medical School and Consultant Physician, Hammersmith Hospital, Du Cane Road, London W12 OHS, United Kingdom

A. Stuart Douglas – Regius Professor, Department of Medicine, University of Aberdeen. Honorary Consultant Physician, Aberdeen Teaching Hospitals, Foresterhill, Aberdeen AB9 2ZD, United Kingdom

Garret A. FitzGerald – Research Fellow, Department of Clinical Pharmacology, Royal Postgraduate Medical School, London. Present address: Department of Medicine and Pharmacology, Vanderbilt University, Nashville, TN 37232, U.S.A.

David C. Flenley – Professor, Department of Respiratory Medicine, City Hospital, Greenbank Drive, Edinburgh EH10 5SB, United Kingdom

John C. Foreman – Division of Clinical Immunology, The Johns Hopkins University School of Medicine at the Good Samaritan Hospital, 5601 Loch Raven Boulevard, Baltimore, MD 21239, U.S.A.

Donald B. Hunninghake – Associate Professor of Medicine and Pharmacology, Department of Pharmacology, 105 Millard Hall, 435 Delaware Street, S.E., University of Minnesota, Minneapolis, MN 55455, U.S.A.

Brian F. Johnson – Professor of Medicine and Pharmacology, Director, Division of Clinical Pharmacology, University of Massachussets Medical School, Worcester, MA 01605, U.S.A.

Gordon M. Lees – Senior Lecturer, Department of Pharmacology, University of Aberdeen, Marischal College, Aberdeen AB9 1AS, United Kingdom

Denis G. McDevitt – Professor, Department of Therapeutics and Pharmacology, The Queen's University of Belfast. Consultant Physician, Belfast City Hospital and Royal Victoria Hospital, Belfast, Northern Ireland

Robert J. Myerburg – Professor of Medicine, Director, Division of Cardiology, University of Miami School of Medicine, Miami, FL 33152, U.S.A.

Philip S. Norman – Professor of Medicine, Division of Clinical Immunology, The Johns Hopkins University School of Medicine at the Good Samaritan Hospital, 5601 Loch Raven Boulevard, Baltimore, MD 21239, U.S.A.

C. P. O'Boyle – Research Fellow, Department of Clinical Pharmacology, Royal College of Surgeons in Ireland, and Blood Pressure Evaluation and Treatment Clinic, The Charitable Infirmary, Jervis Street, Dublin, Ireland

Eoin T. O'Brien – Physician, Blood Pressure Evaluation and Treatment Clinic, The Charitable Infirmary, Jervis Street, Dublin, Ireland

Kevin O'Malley – Professor of Clinical Pharmacology, Royal College of Surgeons in Ireland. Consultant Physician in St. Laurence's Hospital and Charitable Infirmary, Jervis Street, Dublin, Ireland

James C. Petrie – Senior Lecturer, Department of Therapeutics and Clinical Pharmacology, University of Aberdeen. Honorary Consultant Physician, Aberdeen Teaching Hospitals, Foresterhill, Aberdeen AB9 2ZD, United Kingdom

David S. Sheps – Assistant Professor of Medicine, Director Coronary Care Unit, Division of Cardiology, Department of Medicine, University of Miami School of Medicine, Miami, FL 33152, U.S.A.

Paul Turner – Professor, Department of Clinical Pharmacology, St. Bartholomew's Hospital Medical College. Honorary Physician, St. Bartholomew's Hospital, London, United Kingdom

Steven J. Warrington – Lecturer, Department of Clinical Pharmacology, St. Bartholomew's Hospital Medical College, London, United Kingdom

James W. Wynne – Associate Professor, Departments of Medicine and Anesthesiology, University of Florida College of Medicine, P.O. Box J-254, J. Hillis Miller Health Center, Gainesville, FL 32610, U.S.A.

Contents

1

Evaluation of drug interactions

J. C. Petrie and L. E. Cluff

The potential for drug–drug interactions to occur is immense. The thoughtful and careful prescriber who seeks to practise rational drug therapy and to avoid unintentional concurrent prescription of drugs which interact adversely faces major difficulties because thousands of drugs are available, each of which can interact with other drugs. The effects of the innumerable permutations of drug–drug interactions cannot be known to every prescriber. Indeed the possibility of drug interactions is only one of many possible untoward events which doctors must consider in medical practice and the relative importance of drug interactions in medical practice and in the response of individual patients to therapy is not known. The aim of this book is to provide authoritative evaluation, based on clinical pharmacological principles, of the clinically important adverse interactions associated with drugs used in the treatment of some cardiovascular and respiratory diseases. Two further volumes will deal with drugs used in the therapy of other groups of diseases (Petrie and Cluff, in preparation).

We believe that there is a clear need for such information about drug interactions. Many of the available texts provide long lists of terse statements, which necessarily are often based upon anecdotal and poorly validated reports of clinically observed events, in vitro studies or when non-therapeutic doses of drugs are used in patients. In addition, reports of acute, single-dose studies in healthy young volunteers and catalogues of potential interactions do not provide the information doctors need regarding adverse drug effects.

The 12 chapters which follow present the relevant clinical pharmacology related to interactions which are important to the drug groups under discussion. As discussed in a previous volume (Cluff and Petrie, 1975), drug action, adverse reactions and drug interactions are influenced by drug factors such as absorption, distribution,

metabolism, excretion, route of administration, dosage regimens and inter-individual variation. Discussion of such drug factors helps to place interactions involving different drug groups into perspective so that clinically important adverse drug effects involving each drug group can be anticipated and predicted.

The influence of patient or host factors in the evaluation of clinically important adverse drug interactions also merits the most careful consideration. These factors can greatly increase the occurrence of adverse drug reactions. Awareness of clinical determinants of untoward drug effects (Weed, 1971; Cluff et al., 1975) and appropriate tailoring of drug regimens may be very important in the prevention of drug-induced disease. Many factors which affect the efficacy of drugs influence the assessment of the effects of interactions between drugs (Stewart and Cluff, 1975). For example, elderly patients may be at risk because of a reduced ability to metabolise certain drugs (O'Malley et al., 1979) and are more likely than younger patients to suffer from hepatic renal, pulmonary, cardiac and cerebral dysfunction which may affect the handling and response to drugs. Organ dysfunction can profoundly affect drug action and the effects of cardiovascular disease (Thomson, 1974), renal disease (Gibaldi, 1977) and respiratory disease (Du Souich et al., 1978) have been reviewed. Cirrhosis, hypoalbuminaemia and hepatic microsomal dysfunction also affect drug action (Wilkinson and Schenker, 1976). Thyroid disease (Eichelbaum, 1976), genetic factors, environment, biochemical disturbances, nutritional state, pregnancy, circadian rhythms, extremes of temperature also require consideration because of their recognized effects on drug action.

The prescribing patterns of physicians also contribute to the possibility of adverse drug effects including drug interactions. The number of drugs taken by patients at home is directly related to the number of doctors prescribing for each patient, and the larger the number of drugs taken the greater is the probability of occurrence of adverse drug interactions (Stewart and Cluff, 1971).

In hospital and general practice there is a relationship between the number of drugs given to patients and the rate of occurrence of adverse drug reactions (Gardner and Cluff, 1970; Petrie et al., 1975). An important way to avoid the untoward effects of drugs, therefore, is to reduce the number of drugs given to a patient during a particular period of time, and to better monitor and control the drugs given to patients by different physicians. Attention must also be given to drugs not prescribed by doctors but obtained by patients "over the counter." These too can cause adverse drug effects including those attributable to drug interactions (Stewart and Cluff, 1971).

Patients may not take medicines as prescribed or directed. This may result in the failure of a drug in achieving a particular therapeutic effect when the drug is not taken. On the other hand, when taken in a dose or at times which are inappropriate, the drug's pharmacological effect may be exaggerated or absent. For these reasons, how patients use drugs can be a determinant of unwanted adverse consequences. To avoid or reduce this problem doctors should carefully inform patients about how drugs are to be taken, the purpose for which they are given, and the adverse effects which may develop and which should be reported if they occur.

Drugs differ in the frequency with which they are responsible for adverse drug

interactions. Antihypertensive drugs and anticoagulants, for example, appear to be particularly important potential causes of adverse drug interactions (May and Cluff, 1977). Therefore, physicians must be alert to the possibility of such interactions in the treatment of patients with clinical problems requiring the use of particular types of drugs. This is an important reason for the manner of discussing drug interactions in this book.

Adverse drug reactions in patients are usually reported as a result of spontaneously observed clinical events, intensive epidemiological studies, or investigation of a particular drug during clinical trials. Validation of reports from spontaneous clinical observations or epidemiological studies has been exceedingly difficult. Recently, logic trees or algorithms have been developed to provide a uniform basis for determining the probability of a clinical event being attributable to a drug reaction (Hutchinson et al., 1979; Kramer et al., 1979; Leventhal et al., 1979). No fully satisfactory method has yet been developed, however, which will convincingly establish or eliminate many suspected adverse drug effects observed in patients. This complicates the difficulty in the investigation of the clinical effects of drug interactions, and interpretation of the importance of these reactions in medical practice. Furthermore, clinical trials with a drug of necessity are performed in normal individuals and in patients with a particular disease, which require control of the administration of other drugs. Such controlled clinical trials are not often applicable to the circumstances in which drugs are prescribed by doctors in medical practice. The real-life situation in a doctor's office, clinic or hospital is quite different from the conditions of a well-conducted clinical study.

Records kept by doctors of the rationale for drug prescribing, and of all drugs given to patients, are frequently inadequate. Physicians and patients, therefore, often do not have readily available the information they need to monitor what they do and to avoid drug-related problems (Starr and Petrie, 1972; Wilson et al., 1978). Systems have been developed to serve this purpose (Crooks et al., 1967; Erskine et al., 1978; Petrie and McIntyre, 1979) but they are not used as widely and as well as they should be. In part, the failure of doctors to keep adequate medication records is attributable to their seeming lack of awareness or concern about the possibility of drug interactions (Petrie et al., 1974), in spite of evidence suggesting that such interactions are common (Starr and Petrie 1972; Logie et al., 1976).

The ability to predict the possibility of adverse drug interactions is necessary to prevent their happening. To do this well those drugs which are most likely to be involved in drug interactions must be known and the pharmacological basis for their occurrence must be defined. Those patients who are predisposed to adverse drug interactions also must be identified so that drugs which might cause these patients harm can be avoided. The prescribing practices of doctors must be scrutinized by every physician so that those practices which are inappropriate can be recognized and corrected. In addition, doctors should assume more responsibility than is often the case in providing their patients with the information they need to use drugs as prescribed and appropriately. All of these deserve the diligent consideration of clinical pharmacologists and pharmacists. They can play a key role in providing a more rational basis for drug use (Howie et al., 1977; Cluff, 1979). We hope that this

series of volumes on clinically important adverse drug interactions will help pharmacologists, clinicians, pharmacists, and others to understand and control these drug-related problems.

REFERENCES

Cluff, L. E. and Petrie, J. C. (1975) *in*: Clinical Effects of Interaction between Drugs. Excerpta Medica, Amsterdam.

Cluff, L. E., Caranasos, G. J. and Stewart, R. B. (1975) Clinical Problems with Drugs. W. B. Saunders Co., Philadelphia–London.

Cluff, L. E. (1979) Clinical pharmacology, The Forum, Am. Coll. Physicians, 543.

Crooks, J., Weir, R. D., Coull, D., McNab, J. W., Calder, G., Barnett, J. W. and Caie, H. B. (1967) Evaluation of a method of prescribing drugs in hospital and a new method of recording their administration. Lancet, *1*, 668.

Du Souich, P., McLean, A. J., Lalka, D., Erill, S. and Gibaldi, M. (1978) Pulmonary disease and drug kinetics. Clin. Pharmacokin., *3*, 257.

Eichelbaum, M. (1976) Drug metabolism in thyroid disease. Clin. Pharmacokin., *1*, 339.

Erskine, Z. G., Moir, D. C., Jeffers, T. A. and Petrie, J. C. (1978) An outpatient medication record. Br. Med. J., *2*, 1606.

Gardner, P. and Cluff, L. E. (1970) The epidemiology of adverse drug reactions: a review and perspective. Johns Hopkins Med. J., *126*, 77.

Gibaldi, M. (1977) Drug distribution in renal failure. Am. J. Med., *62*, 471.

Howie, J. G. R., Jeffers, T. A., Millar, H. R. and Petrie, J. C. (1977) Prevention of adverse drug interactions. Br. J. Clin. Pharmacol., *4*, 611.

Hutchinson, T. A., Leventhal, J. M., Kramer, M. S., Karch, F. E., Lipmon, A. G. and Feinstein, A. R. (1979) An algorithm for the operational assessment of adverse drug reactions. II. Demonstration of reproducibility and validity. J. Am. Med. Assoc., *242*, 633–638.

Kramer, M. S., Leventhal, J. M., Hutchinson, T. A. and Feinstein, A. R. (1979) An algorithm for the operational assessment of adverse drug reactions 1. Background, description and instructions for use. J. Am. Med. Assoc., *242*, 623–632.

Leventhal, J. M., Hutchinson, T. A., Kramer, M. S. and Feinstein, A. R. (1979) An algorithm for the operational assessment of adverse drug reactions. III. Results of tests among clinicians. J. Am. Med. Assoc., *242*, 1991–1994.

Logie, A. W., Galloway, D. B. and Petrie, J. C. (1976) Drug interactions and long-term antidiabetic therapy. Br. J. Clin. Pharmacol., *3*, 1027.

May, F. and Cluff, L. E. (1977) Drug interactions and multiple drug administration. Clin. Pharmacol. Ther., *23*, 322.

O'Malley, K., Judge, T. G. and Crooks, J. (1979) Geriatric clinical pharmacology and therapeutics. *in*: G. Avery (ed.), Drug Treatment, 2nd ed., p. 158. ADIS Press, Sydney.

Petrie, J. C., Howie, J. G. R. and Durno, D. (1974) Awareness and experience of general practitioners of selected drug interactions. Br. Med. J., *2*, 262.

Petrie, J. C., Durno, D. and Howie, J. G. R. (1975) Drug interaction in general practice. *in*: L. E. Cluff and J. C. Petrie (eds.), Clinical Effects of Interaction between Drugs, p. 237. Excerpta Medica, Amsterdam.

Petrie, J. C. and McIntyre, N. (eds.) (1979) The Problem Orientated Medical Record – its Use in Hospitals, General Practice and Medical Education Churchill Livingstone, Edinburgh.

Starr, K. J. and Petrie, J. C. (1972) Drug interactions in patients on long-term oral anticoagulant and antihypertensive adrenergic neurone-blocking drugs. Br. Med. J., *4*, 133.

Stewart, R. B. and Cluff, L. E. (1971) Studies on the epidemiology of adverse drug reactions. VI. Utilization and interactions of prescription and nonprescription drugs in outpatients. Johns Hopkins Med. J., *129*, 319.

Stewart, R. B. and Cluff, L. E. (1972) A review of medication errors and compliance in ambulant patients. Clin. Pharmacol. Ther., *13*, 463.

Stewart, R. B. and Cluff, L. E. (1975) Methods of study of drug interaction. *in*: L. E. Cluff and J. C. Petrie (eds.), Clinical Effects of Interaction between Drugs, p. 9. Excerpta Medica, Amsterdam.

Thomson, P. D. (1974) Alteration in pharmacologic response induced by cardiovascular disease. *in*: K. L. Melmon (ed.), Cardiovascular Drug Therapy. Davis, Philadelphia.

Weed, L. L. (1971) Medical Records, Medical Education, and Patient Care. The Press of Case Western Reserve University, Cleveland.

Wilkinson, G. R. and Schenker, S. (1976) Effect of liver disease on drug disposition in man. Biochem. Pharmacol., *25*, 2675.

Wilson, L. A., Petrie, J. C., Dawson, A. A. and Marron, A. C. (1978) The new Aberdeen medical record. Br. Med. J., *2*, 414.

Cardiovascular and respiratory disease therapy, edited by J. C. Petrie

2

Drug interactions involving digitalis glycosides

Brian F. Johnson

1. INTRODUCTION

As most patients who take digitalis glycosides continue to take them for many years, there is ample opportunity for interaction with other drugs. Such interactions can be of considerable importance, as there is a relatively small ratio between therapeutic and toxic dosage levels. Whereas the most dramatic evidence of such an interaction may be the precipitation of a life-threatening cardiac arrhythmia, interactions may also reduce the beneficial effects of digitalis with resultant loss of control of heart failure or atrial fibrillation.

The most widely prescribed cardiac glycosides are digoxin, digitoxin, and ouabain. Digoxin and digitoxin may be given parenterally but are most commonly given by mouth. Ouabain must be given intravenously and is usually reserved for emergency situations. All produce a similar pattern of pharmacological effects, the most important being (a) direct stimulation of myocardial contractility, and (b) complex effects upon automaticity and conduction of electrical impulses due to both direct cardiac actions and alteration of autonomic nervous activity. It is known that digitalis glycosides inhibit a magnesium and ATP dependent, sodium and potassium activated transport enzyme complex designated $(Na^+ + K^+)$-ATPase. As this enzyme controls the flux of sodium and potassium across the myocardial cell membrane, digitalis glycosides increase intracellular sodium and decrease potassium content. Smith and Haber (1973) have reviewed the evidence that this is the basic process by which direct myocardial effects are produced. It is believed that increased intracellular sodium increases contractility by causing enhanced calcium concentration around the contractile element. Although relatively little is known about the other sites of digitalis action, such as autonomic nuclei in the brain stem, it appears highly likely that digitalis glycosides share the capacity to activate specific receptors. Hence,

all digitalis glycosides will interact in a similar way with drugs which alter the pharmacological sequelae of digitalis receptor activation.

By contrast, individual digitalis glycosides have unique pharmacokinetic characteristics. Intestinal absorption of digoxin is incomplete, is highly dependent upon formulation characteristics, and probably varies widely between individuals. Less than 25% is bound to plasma proteins, it has a large apparent volume of distribution, and it is mainly eliminated in the urine as unchanged drug. Its rate of elimination is correlated with measures of renal function, and the plasma half-life is about 35 h in patients with normal renal function. By contrast, digitoxin is completely absorbed from the intestine, is 97% bound to plasma proteins, has a much smaller volume of distribution, and is eliminated much more slowly, mainly by metabolism in the liver, with an average plasma half-life of between 7 and 9 days. Most of the characteristics of a newly introduced semi-synthetic digitalis glycoside, beta-methyldigoxin, appear to be intermediate to those of digoxin and digitoxin. These differing characteristics offer opportunities for other drugs to interact uniquely with individual digitalis glycosides. As ouabain is only administered intravenously, and as it is rarely given continuously for several days, there are relatively few opportunities for interaction with drugs that might alter its pharmacokinetic characteristics.

2. PHARMACOKINETIC INTERACTIONS

2.1. Interference with absorption

2.1.1. Antacids

Marked reduction in the absorption of a single oral dose of digoxin has been demonstrated when various antacids are administered concurrently. Several in-vitro studies have demonstrated that magnesium trisilicate has a much higher binding affinity for digoxin than aluminium or calcium salts or other salts of magnesium (Thompson, 1973b; Khalil, 1974). However, Brown and Juhl (1976) found no major difference in the absorption-inhibiting capacity of magnesium trisilicate, aluminium hydroxide, or magnesium hydroxide in 10 normal volunteers. The cumulative recovery of digoxin following a single 0.75 mg dose was reduced by approximately 25% for each antacid by comparison with control experiments. This study provided no evidence that altered gut motility or adsorption of digoxin to antacids could provide an explanation for the interaction. It has not yet been established whether antacid tablets will have the same effect as suspensions, and the relevance of single dose studies to clinical situations is also undetermined. Neither of two magnesium–aluminium silicate antacid tablet formulations significantly lowered steady-state plasma digoxin levels in a group of 9 normal volunteers (Vohringer et al., 1976). However, in patients who need to take digoxin and antacids on a chronic basis, it would be wise to separate the daily times of administration by at least 2 h.

2.1.2. Kaolin and pectin

Commonly used anti-diarrheal preparations containing kaolin and pectin have been shown to strongly adsorb digoxin (Binnion, 1973). In 10 healthy volunteers,

Brown and Juhl (1976) demonstrated about 40% reduction in urinary recovery of orally administered digoxin when kaolin–pectin was given concurrently. Other investigators have shown that the interaction is highly dependent upon the relative times of administration of digoxin and kaolin–pectin. Concurrent administration of a concentrated kaolin–pectin suspension slowed digoxin absorption and produced a mean 62% decrease in extent of digoxin absorbed in 11 subjects. However, extent of absorption was reduced by only 20% if the kaolin–pectin was given 2 h before digoxin, and was unaffected if kaolin–pectin was administered 2 h after digoxin ingestion in 15 other healthy volunteers (Albert et al., 1978). As with antacids, it is not known whether several days treatment with kaolin–pectin influences the steady-state digoxin concentration, but it would be advisable to separate daily administrations by at least 2 h.

2.1.3. Cholestyramine and colestipol

In 6 patients receiving chronic digoxin treatment, concurrent treatment with cholestyramine 4 g every 6 h produced no short-term effect on either steady-state digoxin concentration or faecal or urinary excretion of a dose of tritiated digoxin. Only after months of continuous cholestyramine administration could any increase in faecal output of digoxin be demonstrated (Hall et al., 1977b). Small reductions in rate and extent of digoxin absorption were demonstrated by Brown et al. (1978) in healthy volunteers during single dose or continued cholestyramine administration. Interactions with digitoxin are more relevant. Although this may to some extent reflect the greater binding affinity for digitoxin (Caldwell and Greenberger, 1970), a more important factor is the much greater enterohepatic circulation of digitoxin. Whereas about 25% of absorbed digitoxin takes part in an enterohepatic process in man, this process is essentially negligible for digoxin. Cholestyramine has been used to interrupt the enterohepatic cycle for digitoxin (Caldwell et al., 1971). By preventing reabsorption, it increases the elimination rate and reduces serum concentrations of digitoxin. In a parallel study in groups of 7 subjects, the plasma half-life of digitoxin was 11.5 days in a control group, and 6.6 days in the group receiving cholestyramine (Perrier et al., 1977). The relative effects of cholestyramine and colestipol remains uncertain. Colestipol has a lower binding affinity for digitoxin in aqueous solutions, but a higher affinity in duodenal fluid (Bazzano and Bazzano, 1972). However, colestipol was not found to significantly shorten the plasma half-life of digitoxin in one study (Van Bever et al., 1976). It seems likely that increase in dosage will be required only for patients receiving digitoxin in whom chronic treatment with cholestyramine becomes necessary (see also Chapter 6).

2.1.4. Sulphasalazine

One study in 10 healthy volunteers suggested that previous administration of 2–6 g sulphasalazine daily for 6 days may reduce the intestinal absorption of a single orally administered dose of digoxin by about 20% (Juhl et al., 1976). The relevance to clinical situations is unknown.

2.1.5. Neomycin

In small groups of healthy volunteers, it has been demonstrated that 1–3 g doses of neomycin may inhibit the extent of intestinal absorption of concurrently administered, single doses of digoxin by about 40% (Lindenbaum et al., 1976). Rate of absorption is also inhibited. Doses of neomycin may reduce absorption of digoxin administered up to 6 h later. In 5 subjects who took digoxin and neomycin concurrently for 9 days, a 28% reduction in steady-state plasma digoxin level was demonstrated. It has been suggested that neomycin impairs the general absorptive processes of the intestinal mucosa.

2.1.6. Other drugs

Other drugs which have been suggested to inhibit digoxin absorption under certain circumstances include activated charcoal (Hartel et al., 1973) and phenytoin (Lahiri and Ertel, 1974). In general, drugs which inhibit digoxin absorption may be responsible for unanticipated loss of therapeutic effect. Conversely, patients who are digitalized while taking one of the above drugs, may develop evidence of toxicity when concurrent drug treatment is stopped.

2.2. Altered bowel motility

2.2.1. Metoclopramide and propantheline

In one study (Manninen et al., 1973), metoclopramide reduced steady-state serum digoxin levels, presumably by diminishing absorption as a result of increased intestinal motility. Similarly, propantheline increased serum levels, presumably by diminishing intestinal motility. However, it is important to note that digoxin tablets of low dissolution rate were used, and that in most parts of the world such tablets have been replaced by formulations from which digoxin is released relatively quickly. With better quality tablets it has been demonstrated that metoclopramide and propantheline cause no clinically important interaction (Johnson et al., 1978).

2.3. Altered protein binding

As little digoxin is bound to plasma proteins, drugs which alter protein binding do not interact. Although digitoxin is extensively bound to serum albumin, the binding affinity is strong and displacement is not readily obtained. High concentrations of phenylbutazone, warfarin, clofibrate (see Chapter 6), sulphonamides, and tolbutamide are capable of displacing digitoxin from albumin (Solomon et al., 1971). However, this seems to be of no clinical significance, as therapeutically observed concentrations of the above agents showed little effect.

Heparin given during haemodialysis releases large quantities of free fatty acids into the circulation, and the clinical relevance of resultant alteration of digitoxin binding has not been determined (Storstein, 1977).