CLINICAL USE OF DRUGS IN RENAL FAILURE

Second Printing

ROBERT J. ANDERSON, M.D.
Assistant Professor of Medicine
Research and Teaching Scholar of
American College of Physicians
Department of Medicine
University of Colorado Medical Center
Denver, Colorado

JOHN G. GAMBERTOGLIO, Pharm. D.
Assistant Clinical Professor of Pharmacy
Division of Clinical Pharmacy
School of Pharmacy
University of California, San Francisco
San Francisco, California

ROBERT W. SCHRIER, M.D.
Professor of Medicine
Head, Division of Renal Diseases
Department of Medicine
University of Colorado Medical Center
Denver, Colorado

With the advent of hemodialysis as a method of sustaining life there has been increased study of drugs used in the treatment of renal failure. This volume serves as a comprehensive drug reference source including in its discussion the pharmacology, adverse effects, dialysis properties and appropriate dosage modifications required for renal failure patients.

This book will be of special value to physicians, paramedical personnel and medical students caring for patients with renal failure. This material will also be of use to internists, pediatricians, nephrologists, urologists, general practitioners and pharmacologists/pharmacists.

CHARLES C THOMAS • PUBLISHER • SPRINGFIELD • ILLINOIS

CLINICAL USE OF DRUGS IN RENAL FAILURE

Second Printing

By

ROBERT J. ANDERSON, M.D.
Assistant Professor of Medicine
Research and Teaching Scholar of American College of Physicians
Department of Medicine
University of Colorado Medical Center
Denver, Colorado

JOHN G. GAMBERTOGLIO, Pharm. D.
Assistant Clinical Professor of Pharmacy
Division of Clinical Pharmacy
School of Pharmacy
University of California, San Francisco
San Francisco, California

ROBERT W. SCHRIER, M.D.
Professor of Medicine
Head, Division of Renal Diseases
Department of Medicine
University of Colorado Medical Center
Denver, Colorado

CHARLES C THOMAS • PUBLISHER
Springfield • Illinois • U.S.A.

Published and Distributed Throughout the World by
CHARLES C THOMAS • PUBLISHER
Bannerstone House
301-327 East Lawrence Avenue, Springfield, Illinois, U.S.A.

ISBN 0-398-03400-1

Library of Congress Catalog Card Number: 74-32187

First Printing, 1976
Second Printing, 1978

With THOMAS BOOKS *careful attention is given to all details of manufacturing and design. It is the Publisher's desire to present books that are satisfactory as to their physical qualities and artistic possibilities and appropriate for their particular use.* THOMAS BOOKS *will be true to those laws of quality that assure a good name and good will.*

Printed in the United States of America
R-11

Library of Congress Cataloging in Publication Data

Anderson, Robert James, 1943-
Clinical use of drugs in renal failure.

Bibliography: p.
Includes index.
1. Renal pharmacology. I. Gambertoglio, John G., joint author. II. Schrier, Robert W., joint author. III. Title. [DNLM: 1. Drug therapy. 2. Kidney failure, Acute—Complications. 3. Kidney failure, Chronic—Complications.
WJ300 A549c]
RM375.A53 615'.761 74-32187
ISBN 0-398-03400-1

CLINICAL USE OF DRUGS IN RENAL FAILURE

To our Wives
Cheryl, Mary and Barbara

PREFACE

THE GENESIS OF THIS BOOK evolved while this author was preparing a talk on "Drugs and Renal Failure" at the University of California, San Francisco. The need for such a book on this topic was apparent, but the task seemed immense. From this talk came a request by two fourth-year students in the School of Pharmacy, John Gambertoglio and Lawrence Fleckenstein, to take an elective on the Renal Service, even though the elective was generally reserved for medical students. Their enthusiasm seemed to merit the opportunity. During their elective on the Renal Service the beginnings of a monograph on the clinical use of drugs in renal failure arose.

With this author's move to the University of Colorado, however, these beginnings were allowed to be dissipated and became outdated. Indeed, these beginnings would have died had it not been for the exceptional enthusiasm, vigor and hard work of one of the present authors, Dr. Robert Anderson, who was a Renal Fellow with us at the University of Colorado Medical Center. It is thus by design, not by alphabetical happenstance, that Dr. Anderson is the first author of this book.

Unfortunately, because of his new responsibilities as a faculty member in the School of Medicine at the University of Rochester, Larry Fleckenstein was unable to work with us on the present book. We, however, do want to thank him for his initial contributions which stimulated the present book. Our gratitude also is extended to two experts in the field, Dr. Ralph Cutler, University of Washington School of Medicine, and Dr. William Bennett, University of Oregon School of Medicine, who were kind enough to review the manuscript for us. We appreciated and incorporated their suggestions. The excellent secretarial assistance of Linda Benson and Diana Davis also was indispensable in the preparation of the manuscript.

We hope that the information compiled in this book will assist physicians in taking care of their patients with renal failure who are receiving drugs—for this is the main purpose of the book. It will also be gratifying if the book serves to provide source material for physicians, pharmacists, medical and pharmacy students.

ROBERT W. SCHRIER, M.D.

CONTENTS

CLINICAL USE OF DRUGS IN RENAL FAILURE

Chapter 1

INTRODUCTION

THE PATIENT WITH RENAL FAILURE is more predisposed to a variety of illnesses than the individual with healthy kidneys. For example, hypertension, cardiac failure, neuropathy, bone disease, infection, anemia and coronary artery disease occur more frequently in patients with renal failure. These patients with kidney disease thus, generally, receive more pharmacological agents to treat their renal and nonrenal related illnesses as compared to individuals with normal kidney function. In addition to receiving more drugs, the patient with advanced renal failure may respond to a given dose of a pharmacological agent, with respect to efficacy and adverse effects, in a substantially different manner than the subject with healthy kidneys. Such different responses in patients with renal failure may be due to abnormalities in urinary excretion, metabolism and/or sensitivity to drugs (Table I).

TABLE I

CAUSES OF DRUG TOXICITY IN RENAL FAILURE

I. Impaired Renal Excretion
II. Impaired Metabolism
III. Increased Sensitivity
  A. Decreased Plasma Protein Binding
  B. Abnormal Blood-Brain Barrier
  C. Alterations in Target Organs

Increased Sensitivity to Drugs in Renal Failure

There are several factors which may be involved in increased sensitivity to drugs in patients with renal failure. For example, a decrease in protein binding of insulin and morphine has been suggested to account for increased sensitivity to morphine and insulin in renal failure. Conversely, a diminished sensitivity to dilantin in renal failure may occur; since although the protein binding is decreased, the drug's half-life is shortened. An abnormal blood brain barrier also

seems to be present in uremia since substances such as bromide, uric acid and creatinine may occur in higher concentrations in the cerebrospinal fluid. Thus, increased penetration into the central nervous system may account for increased sensitivity of some drugs in chronic renal failure. An alteration in target organs (Table II) may

TABLE II

ALTERATIONS IN TARGET ORGANS IN UREMIA

I. Inflammatory and ulcerative changes in gastrointestinal tract provide setting for local irritation of drugs.
II. Increased susceptibility to agents that increase myocardial irritability.
III. May need larger and more toxic doses of diuretics due to decreased glomerular filtration.

also increase the sensitivity to drugs in renal failure. Local irritative properties of drugs may be more pronounced because of inflammatory and ulcerative changes which may occur in the gastrointestinal tract in uremia. So-called uremic myocardiopathy has also been proposed to account for increased myocardial irritability to drugs in renal failure. The effects of uremia on the function of the central nervous system may also predispose to increased drug toxicity on this organ system. Larger, and thus potentially more toxic, doses of diuretics are also necessary in advanced renal failure.

Incidence of Adverse Effects to Drugs in Renal Failure

The clinician might suspect that drug treatment of patients with renal failure is a potentially dangerous undertaking which may be associated with a number of complications. The incidence of drug toxicity in one series has been reported to be two and one-half times greater in patients with blood urea nitrogen (BUN) concentrations in excess of 40 mg/100 ml as compared to subjects with levels of BUN less than 20 mg/100 ml.[1] In another series of 131 patients with renal failure who had a variety of central nervous system symptoms, fifty (31%) of the patients had these symptoms primarily because of drug intoxication.[2] In fact, drug toxicity was the leading single cause of these central nervous system abnormalities.

Drug toxicity, therefore, should be suspected as a potential causative factor in any change in the clinical status of patients with renal failure. The diagnosis of drug-related symptoms may be very difficult, however, since many of these symptoms may be similar to those related to the uremic state. In this regard, gastrointestinal symptoms,

such as anorexia, nausea and vomiting, and central nervous system symptoms, such as obtundation, inability to concentrate, and even coma, are drug-related effects which may mimic the symptoms of uremia.

In addition to drug-related central nervous system and gastrointestinal symptoms, another significant drug-induced hazard in patients with renal failure is further deterioration of renal function. Primarily because of its high blood flow, high metabolic rate and multiple enzymatic processes, the kidney is particularly predisposed to toxicity (Table III). Often, a vicious cycle occurs whereby im-

TABLE III

VULNERABILITY OF THE KIDNEY TO NEPHROTOXIC AGENTS

I. Large Blood Flow (25% cardiac output)
II. High Metabolic Activity
III. Large Endothelial Surface
IV. Many Enzyme Systems
V. Countercurrent System Raises Medullary Concentration
VI. Mechanisms for Protein Unbinding

paired renal excretion leads to increased plasma concentrations and prolonged half-lives of the toxic drug and further kidney damage. In Table IV are listed some of the drugs which may cause renal damage either by a direct nephrotoxic effect or secondary to a hypersensitivity reaction.

Metabolic Loads with Drug Therapy in Renal Failure

Not only may drugs cause nephrotoxicity, but also several drugs contain significant amounts of sodium, magnesium and other substances capable of aggravating the already precarious fluid/electrolyte and acid/base balance of patients with renal impairment. Various antacids and other drugs contain significant amounts of electrolytes which are not readily excreted by the diseased kidney. Excessive use of antacids in patients with advanced renal failure can lead to sodium accumulation and expansion of extracellular fluid volume, hypermagnesemia and hypercalcemia. In Table V are shown drugs which contain significant amounts of sodium. Some forms of penicillin may also contain significant amounts of potassium, as do salt substitutes. Exchange resins which are used to treat hyperkalemia may also lead to sodium or calcium retention depending on the nature of the resins. A hydrogen ion load can also be administered to

TABLE IV

SOME DRUGS WHICH MAY BE NEPHROTOXIC OR INITIATE RENAL DISEASE SECONDARY TO HYPERSENSITIVITY REACTIONS

Direct Nephrotoxicity	*Toxicity Due to Hypersensitivity*
Gentamicin	Penicillins
Kanamycin	Sulfonamides
Neomycin	Rifampin
Streptomycin	Furosemide
Polymixins	Azathioprine
Vancomycin	Allopurinol
Bacitracin	Trimethadione
Cephalosporins	
Tetracyclines	
Sulfonamides	
Pentamidine	
Viomycin	
Capreomycin	
Amphotericin B	
Gold	
Bismuth	
Mercurials	
Penicillamine	
EDTA	
Phenylbutazone	
Indomethacin	
Phenacetin	
Paracetamol	
Salicylates	
Phenazone	
Aminophenazone	
Pyridium	
Methotrexate	
Methoxyflurane	

the patient with renal failure in the form of ammonium chloride, ascorbic acid, mandelamine and metabolites of nitrofurantoin. In Table VI are summarized some of the metabolic loads which may occur during administration of various drugs in patients with renal failure.

Elimination Half-Life, Volume of Distribution and Protein Binding of Drugs

In this book no attempt will be made to present a detailed description of the kinetic analysis of drugs; however, several basic concepts will be discussed briefly to better allow the physician to deal with information about drug therapy in patients with renal failure. The most frequent means of expressing the rate of removal of a drug

TABLE V

SODIUM CONTENT OF COMMONLY USED DRUGS

Ampicillin	3.0 mEq/gm
Carbenicillin	4.7 mEq/gm
Cephalothin	2.4 mEq/gm
Chloramphenicol	2.3 mEq/gm
Erythromycin	3.0 mEq/250 mg
Methicillin	3.0 mEq/gm
Oxacillin	2.5 mEq/gm
Para-aminosalicylic acid	2.3 mEq/gm
Penicillin G	1.7 mEq/million units
Dimenhydrinate (Dramamine®)	2.5 mEq/tab
Heparin	1.5 mEq/10 ml
Fleets phosphasoda	24.0 mEq/5 ml
Fleets sodium phosphate	213.0 mEq/5 oz
Sodium polystyrene sulfonate (Kayexalate®)	67.0 mEq/16 gm
Antacids	(see Table XVIII)

TABLE VI

METABOLIC LOADS CAUSED BY DRUGS

I. Magnesium—antacids, laxatives or antihypertensive medications
II. Potassium—salt substitutes and massive penicillin G (potassium salt) therapy
III. Sodium—antacids, sodium-potassium exchange resins, large doses of penicillin G (sodium salt), carbenicillin, ampicillin
IV. Calcium—calcium exchange resins, antacids
V. Phosphate—enemas, antacids
VI. Antianabolic—tetracycline, adrenal steroids
VII. Uric acid—chemotherapeutic destruction of neoplastic tissue, diuretic agents
VIII. Alkalosis—absorbed antacids ($NaHCO_3$, $CaCO_3$), large doses of penicillin and carbenicillin may enhance hydrogen ion excretion
IX. Acidosis—ammonium chloride, ascorbic acid, PAS, isoniazid, phenformin, mandelamine, metabolism of nitrofurantoin

from the body is the use of the expression *elimination half-life*.[3,4] Elimination half-life may be defined as the time required for the amount of drug in the body to decline by one-half.[5] This is usually determined by measurements of the blood or plasma concentration after equilibration of the drug distribution between plasma and tissue has been achieved. The percent of drug remaining in the body after one, two, three, four and five half-lives is 50, 25, 12.5, 6.25 and 3.13 percent respectively. Thus 97 percent of an administered dose is eliminated by five half-lives. Drug elimination from the body may be achieved either by excretion of unchanged drug or conversion to metabolites which may be active or inactive.

Other than the rate at which a drug is excreted or metabolized, the volume in which the drug is distributed within the body is an-

other important determinant of elimination.[6] Rowland[5] defines the volume of distribution "as that volume into which the drug appears to distribute with a concentration equal to that in blood." This apparent "volume of distribution" of a drug is calculated by dividing the amount of drug in the body by its plasma or blood concentration. The volume of distribution is generally not a specific anatomical compartment of the body, but rather an expression which represents the distribution of a drug in various body fluids and tissues. In general, the volume of distribution depends upon the degree of protein binding of the drug and its relative water and lipid solubility. Drugs that are highly protein bound generally have a smaller volume of distribution, while drugs that are highly lipid soluble penetrate readily into body tissues and generally have a large volume of distribution. There are, however, exceptions to these general guidelines.

In addition to its effect on the volume of distribution of drugs, the degree of protein binding may also influence the action of drugs. The degree of protein binding of certain drugs can be altered in renal failure.[7,8] Generally, the unbound drug is considered the pharmacologically active moiety. In addition, the protein bound fraction of the drug is not readily filtered or dialyzed. Prominent examples of alterations in protein binding of drugs in patients with renal disease include the decreased protein binding of diphenylhydantoin,[7] sulfamethoxazole,[8] dicloxacillin[8] and morphine.[7]

Effect of Renal Failure on Gastrointestinal Absorption of Drugs

It is important to consider several potential consequences of renal failure on drug absorption. Malabsorption of some substances from the gastrointestinal tract such as calcium and iron, may occur in the presence of advanced renal failure. With respect to calcium malabsorption, the failure of the conversion of vitamin D to its active form, 1,25-dihydroxy vitamin D_3, by the diseased kidney is perhaps the primary factor.[9] The exact mechanism for the malabsorption of iron has not been as clearly defined. It is known, however, that the absorption of iron, as well as various drugs, is related to gastric acidity. The effect of the internal urea-ammonia cycle which occurs in the azotemic patient may be quite important with respect to the level of gastric acidity (Fig. 1). With the occurrence of azotemia,

INTERNAL AMMONIA–UREA CYCLE

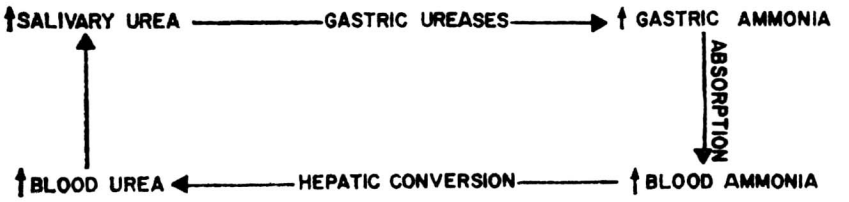

Figure 1.

the salivary concentration of urea increases and in the presence of gastric ureases, an increase in ammonia occurs which buffers the gastric hydrochloric acid and thereby increases gastric pH. Thus, iron and drugs which are best absorbed in an acidic environment may have impaired absorption in azotemic patients. Since the increased gastric ammonia is absorbed and converted to urea in the liver, a continuous cycle of increased salivary urea concentration and gastric ammonia occurs. In addition to the effect of ammonia on gastric or intestinal acidity, the irritative effect of ammonia probably contributes to the syndromes of uremic stomatitis, gastritis and colitis and perhaps even pancreatitis, all of which could contribute to drug malabsorption.

Renal Excretion of Drugs

It is also very important to discuss the modes of drug excretion by the kidney. Renal excretion is the primary pathway for the elimination of various drugs and there are several means of drug handling by the kidney, including glomerular filtration, active reabsorption, tubular secretion and nonionic back diffusion (Table VII). The rate of glomerular filtration of drugs depends in large part on their degree of protein binding. Since most drugs are at least partially protein bound, their filtration rates are less than glomerular filtration rate. Some agents, such as fluoride, bromide and lithium, are both filtered and actively reabsorbed by the proximal tubules. Maneuvers which decrease proximal tubular reabsorption, such as saline infusion, proximal tubule diuretics (e.g. acetazolamide) and osmotic diuresis, therefore increase the renal clearance of bromide, lithium and fluoride. Conversely, volume depletion and sodium restriction enhance the tubular reabsorption of