Drug Dosage
The authors and the publisher have exerted every effort to ensure that drug selection and dosage set forth in this text are in accord with current recommendations and practice at the time of publication. However, in view of ongoing research, changes in government regulations, and the constant flow of information relating to drug therapy and drug reactions, the reader is urged to check the package insert for each drug for any change in indications and dosage and for added warnings and precautions. This is particularly important when the recommended agent is a new and/or infrequently employed drug.

All rights reserved.
No part of this publication may be translated into other languages, reproduced or utilized in any form or by any means, electronic or mechanical, including photocopying, recording, microcopying, or by any information storage and retrieval system, without permission in writing from the publisher.

Copyright 1992 by S. Karger AG, P.O. Box, CH-4009 Basel (Switzerland)
Printed in Switzerland on acid-free paper by Thr AG Offsetdruck, Pratteln
ISBN 38055-5360-9

To my wife, Matilde, for her love and understanding.
Her constant patience and encouragement helped me along the road towards editing this book.

Contents

Foreword by G.N.J. Tytgat IX
Preface XI

Introduction

Heading, R.C.; Eaves, N.R. (Edinburgh): Aims of Treatment in Gastroesophageal Reflux Disease 1

Motor-Stimulating Drugs

Castell, D.O. (Philadelphia, Pa.): Gastroesophageal Reflux Disease Is a Motility Disorder 11
Johnson, A.G. (Sheffield): Domperidone in the Treatment of Gastroesophageal Reflux Disease 45
Corazziari, E.; Bontempo, I. (Rome): Cisapride in Gastroesophageal Reflux Disease: Effect on Esophageal Motility and Intraesophageal pH 64
Corinaldesi, R.; Stanghellini, V.; De Giorgio, R.; Barbara, L. (Bologna): Cisapride in Gastroesophageal Reflux Disease: Effect on Gastric Emptying and Clinical Results 70

Contents VIII

Acid-Lowering Drugs
Dammann, H.G. (Hamburg): Treatment of Gastroesophageal Reflux Disease with Ranitidine 208
Bovero, E.; De Iaco, F. (Genoa); Iaquinto, G. (Avellino); Poletti, M. (Genoa); Zambelli, A. (Crema); Cheli, R. (Genoa): Famotidine and Gastroesophageal Reflux Disease 231
Bardhan, K.D. (Rotherham): Omeprazole in the Treatment of Gastroesophageal Reflux Disease 246

Mucosal Protective Agents
Dajani, E.Z. (Chicago, Ill.): Prostaglandins and the Integrity of the Esophageal...
Foreword

Gastroesophageal reflux disease (GERD) has been at the forefront of basic and clinical research over the last decade. The spectrum of the clinical presentation of GERD is wide, ranging from mild intermittent reflux symptoms without mucosal damage to chronic unrelenting heartburn and regurgitation associated with major histological change and occasionally complications. Pharmacology has witnessed an explosive growth in reflux-related development, in particular through the widespread clinical application of H2 receptor antagonists, proton pump inhibitors, and prokinetics. Till now almost all the relevant information has been published in separate manuscripts or in overviews appearing in supplements to various journals. In view of the large body of information and its dispersed nature in the literature, Prof. Scarpignatatos initiative to put all the information together was more than timely and highly appropriate. This volume indeed reflects the state of affairs of clinical pharmacology in reflux disease. The style is critical, objective and encyclopedic.

Before the detailed analysis of all pharmacological principles, the aims of pharmacotherapy in reflux disease are first discussed. Those aims are threefold: alleviation of symptoms, resolution of mucosal damage and inflammation together with the prevention of complications, and prevention of recurrent disease. It is interesting to read that a subjective scoring of the quality of life is launched as an important parameter of symptomatic evaluation in all future trials. The first major category of drugs, analyzed in depth, consists of the motor-stimulating compounds. They are discussed after a thoughtful introductory overview of the underlying motor abnormalities in GERD. This is then followed by an in-depth analysis of the pharmacology and clinical applicability of the various motor-modulating
drugs used in clinical practice: metoclopramide, clebopride, domperidone, cisapride, 5-HT3 receptor antagonists, cholecystokinin antagonists, erythromycin and the motilides. Particular emphasis is given to cisapride, the currently best investigated and clinically most useful prokinetic. The second major category of compounds discussed in depth consists of the acid-neutralizing or acid-lowering drugs: antacids, alginates, selective anti-muscarinic agents, H2 receptor antagonists (cimetidine, ranitidine, famotidine, nizatidine), and, lastly, proton pump inhibitors, in particular omeprazole. Obviously, the H2 receptor antagonists and omeprazole attract most of the attention, which is readily explained by their widespread clinical application. The last category consists of the mucosal protective agents, prostaglandins and especially sucralfate.

After reading through the chapters one cannot resist the temptation to draw the attention of the reader to some of the peculiarities of this little bible. Indeed, the reader is struck by some original observations and thoughtful comments scattered throughout the monograph and made by experts from all over the world. One is also surprised by the encyclopedic character of the various manuscripts giving a detailed and thorough account of the currently available literature. Yet the text flows well because a lot of data are put together carefully in easily readable tables. Finally, it is interesting to see that many of the chapter authors commented upon the difficulties of comparing different studies. There is an urgent need for a consensus on the selection criteria of patients with GERD before entering future trials, for a consensus on the methodology to score and analyze reflux-related symptoms, and for a consensus on the grading of reflux-induced mucosal damage. Only then will it be possible to compare the various therapeutic principles and to analyze the potential benefit of combination therapy.

Prof. Scarpignato is to be congratulated for superbly editing this volume on the therapy of reflux disease. He must have spent many hours in putting all these chapters together in such an excellent uniform design and style. His dedication is exemplary for all of us. This book will undoubtedly become 'the' standard reference book for years to come, because it contains a wealth of information in an appropriately designed format. It is to be hoped that this monograph will play a useful role in further stimulating the interest of clinical and basic researchers alike in this important area of medicine which is gastroesophageal reflux disease.

Amsterdam, November 1991Prof. Dr. G.N.J. Tytgat

Preface
The considerable growth of interest and developments in the field of esophageal disease have been reflected in recent years by the many symposia held and books published on the topic. Gastroesophageal reflux disease (GERD) is a very common disorder bringing a large number of patients to physicians every day. It has indeed replaced peptic ulceration as one of the most frequently encountered disorders of the upper gastrointestinal tract in the Western hemisphere. In the early 1970s, treatment of the disease consisted mainly of antacids and lifestyle modifications, but recently developed agents have changed the management strategy. Many patients have only minor and intermittent symptoms with no esophageal damage, some display frequent symptoms with different degrees of lesions and a few present with the complications of the disease. It is fairly obvious that for each of them a different pharmacological approach is needed. However, the many drugs available today create some difficulty for the physician who must write a prescription for his or her patient. One is therefore justified in making a critical overview of all the available compounds in an attempt to find out for each class of drugs and even for each compound the right place in the therapeutic armamentarium. To this end, I have asked leading experts in the field, known for their direct personal experience and scientific expertise, to compile a series of reviews to synthesize the mass of general and scientific information existing in the field. Most of them participated at two Round Tables I organized during the International Symposium on Esophageal Disease which took place in Sicily a few years ago and there they already did a great job. I am indebted to all of them for accepting to share with us their knowledge and for providing me with excellent manuscripts, despite the many daily commitments.

Preface

The first chapter of the book deals with a very crucial point of management, that is the aims of GERD treatment. The chapters that follow (assembled in two different sections) describe the relevant pharmacology and mechanism of action of each motor-stimulating drug and acid-lowering compound and also evaluate their place in the management of GERD. In each section, an introductory chapter is supplied with the aim of providing the pathophysiological background for the use of each class of drugs. A separate section covers the role of mucosal protective agents in the treatment of the disease. Finally, the last section is devoted to special topics, namely assessment of healing and long-term management of healed reflux esophagitis.

Editing a book is always a very difficult task. Although I have tried my best to control it, I am still guilty of some repetition, almost inevitable in a
multi-author work. I hope it will be looked upon as educational reinforcement rather than poor editing. It cannot be expected that this volume will quiet all controversies; however, data are presented that should aid any practitioner in making therapeutic decisions. It is my hope that this book, which includes much of the information difficult to collect from other scattered sources, will be a valuable reference text for gastroenterologists, digestive surgeons and all doctors who are engaged in the management of this very common, multifactorial disorder.

In addition to the outstanding authors, this book would not have been possible without the efforts of some key persons who supported this work. I wish here to express my appreciation to Mrs. Denise Greder, of S. Karger AG, Medical and Scientific Publishers, Basel, for her advice and understanding, and to Miss Anke Rogal for her remarkable work of supervision and editorial production. Warmest thanks must go also to my secretary, Sabina Cavagni, for her neverfailing enthusiasm and inexhaustible efforts during the editorial work.

Parma, October 1991Carmelo Scarpignato