Edited by
David H. Lawson and R. Michael E. Richards

CLINICAL PHARMACY

and Hospital Drug Management

Clinical Pharmacy and Hospital Drug Management

DAVID H. LAWSON
M.D., F.R.C.P., F.C.P.
Consultant Physician, Glasgow Royal Infirmary
Visiting Professor, School of Pharmaceutical Sciences,
University of Strathclyde, Glasgow

and

R. MICHAEL E. RICHARDS
B.Pharm., Ph.D., F.P.S.
Senior Lecturer in Pharmaceutics,
University of Strathclyde, Glasgow

LONDON
CHAPMAN AND HALL

First published 1982
by Chapman and Hall Ltd
11 New Fetter Lane London EC4P 4EE

Printed in Great Britain by
The University Press, Cambridge

ISBN 0 412 22760 6

British Library Cataloguing in Publication Data

Clinical pharmacy and hospital drug management.
1. Chemotherapy
I. Lawson, David H.
II. Richards, R. Michael E.
615.5'8 RM262

ISBN 0-412-22760-6

Contributors

J.A. Baker, B.Pharm., F.P.S.
Area Pharmaceutical Officer, Kensington, Chelsea and Westminster Area Health Authority, London

C.W. Barrett, M.Pharm., M.P.S.
Area Pharmaceutical Officer, The City and East London Area Health Authority

N.D.S. Bell, B.Sc., F.P.S.
Lecturer in Pharmaceutics, University of Strathclyde, Glasgow

S.M. Bryson, B.Sc., M.Sc., M.P.S.
Staff Pharmacist, Clinical Pharmacy, Stobhill General Hospital, Glasgow

G. Calder, B.Sc., F.P.S., M.I.Pharm.M.
Deputy Chief Pharmacist, Department of Health and Social Security, London

J.A. Farwell, B.Pharm., Ph.D., M.P.S.
Area Pharmaceutical Officer, St Bartholomew's Hospital, London

A.F. Fell, B.Pharm., Ph.D., M.P.S., C.Chem., M.R.S.C.
Lecturer in Pharmaceutical Analysis, Heriott-Watt University, Edinburgh

A.T. Florence, B.Sc., Ph.D., A.R.C.S.T., C.Chem., F.R.S.C., M.P.S.
Professor of Pharmaceutics, University of Strathclyde, Glasgow

P. Horton; B.Sc., Ph.D.
Principal Physicist, Department of Clinical Physics and Bio-Engineering, West of Scotland Health Boards, Glasgow

D.H. Lawson, M.D., F.R.C.P., F.C.P.
Consultant Physician, Glasgow Royal Infirmary.
Visiting Professor, School of Pharmaceutical Sciences, University of Strathclyde, Glasgow

J. McCabe, M.P.S.
Principal Pharmacist, Glasgow Royal Infirmary, Glasgow

C.B. Macfarlane, B.Sc., Ph.D., C.Chem., M.R.S.C., M.P.S.
Director of Pharmaceutical Development, Syntex Research Centre, Edinburgh

I.W. Marshall, B.Sc., M.P.S.
District Pharmaceutical Officer, St James' University Hospital, Leeds

L.G. Moonie, M.B., M.R.C. Psych.
Clinical Pharmacologist, Syntex Research Centre, Edinburgh

R.M.E. Richards, B.Pharm., Ph.D., F.P.S.
Senior Lecturer in Pharmaceutics, University of Strathclyde, Glasgow
Formerly Professor of Pharmacy, University of Rhodesia, Salisbury, Rhodesia

E.G. Salole, B.Sc., Ph.D., M.P.S.
Lecturer in Pharmaceutics, University of Strathclyde, Glasgow

G.G. Skellern, B.Sc. Ph.D., C.Chem., M.R.S.C.
Lecturer in Pharmaceutical Chemistry, University of Strathclyde, Glasgow

G.A. Smail, B.Sc., Ph.D., A.R.C.S.T., F.P.S.
Senior Lecturer in Pharmaceutical Chemistry, University of Strathclyde, Glasgow

W.J. Tilstone, B.Sc., Ph.D., M.R.C. Path.
Professor of Forensic Science, University of Strathclyde, Glasgow

A.R. Willson, B.Pharm., M.P.S.
Staff Pharmacist, Westminster Hospital, London

Foreword

It gives me great pleasure to write a foreword for this book, as it deals with subjects in which I have been interested for many years. One of the editors, Dr Richards, did his postgraduate pre-registration studentship with me, and I believe that he and Professor Lawson have performed a valuable service to pharmacy and medicine in writing and editing the book, in collaboration with a distinguished and experienced team of contributors.

The profound influence that formulation can have on drug action was brought to my attention in the 1950s, before the terms *bioavailability* and *biopharmaceutics* were coined, by several instances at University College Hospital where poor clinical results were shown to have been caused by unsuitable formulation.

The subject is now realized to be one of great importance and the chapter by Professor Florence and Dr Salole provides a concise summary of its relevance.

As a participant in both the 1961 and 1969 World Health Organization Conferences on Quality Control, in the developments leading up to the passing and implementation of the *Medicines Act* and the deliberations of the Rosenheim Committee, I am especially aware of the need for strict quality assurance in hospital as well as in other branches of pharmacy. Dr Fell's chapter covers the evolution of quality assurance concepts in hospital pharmacy and gives a valuable guide to their adoption as an integral part of a modern hospital pharmaceutical service.

The introduction of clinical pharmacy has done much to bring pharmacists into closer touch with prescribers and with the details of the treatment of patients. To be successful it must be soundly based on knowledge of biopharmaceutics, pharmacokinetics and metabolism and the chapters on those and related subjects by Professor Tilstone and Dr Skellern have outlined the roles of such

subjects in clinical pharmacy. The former discusses the effects of bioavailability and of dosage regimens on blood levels and the pharmacokinetic significance of body drug distribution. The latter outlines the role of enzymes in drug metabolism, discussing the factors affecting it including environmental chemicals, drugs and diet and also genetic, physiological and pathological factors.

Investigations over the past two decades have revealed how frequently patients fail to take their medicines in accordance with their medical advisers' instructions and the term non-compliance has been coined for this subject. Mr Bryson and Professor Lawson give a precise definition of non-compliance and discuss its extent, importance and methods of assessment. They analyse the major reasons for patients failing to comply with directions as well as giving valuable information on strategies for improving compliance. The importance of this subject cannot be overemphasized. All the scientific knowledge and professional care of physicians, pharmacists and their colleagues are wasted if patients fail to take their medicines or do so in a way which prevents or seriously reduces their effects. It is also a subject in which pharmacists can and should play a vital role and one where relatively simple procedures can cause great improvements.

Whilst, for many years, the major manufacturing pharmaceutical firms have usually paid considerable attention to the testing of new drugs, greater emphasis on the need for extensive animal and clinical trials of such substances resulted from the thalidomide tragedy and other serious adverse reactions such as those caused by practolol. The former undoubedly accelerated the introduction of the *Medicines Act* which made animal tests and clinical trials compulsory and under which regulations have been made to guide persons undertaking them.

Drs Macfarlane and Moonie outline the design of clinical trials and they rightly stress the importance of dosage forms for the comparability of performances of preparations and of ensuring compliance with instructions for taking them by the volunteer participants. Both factors profoundly affect the validity of the trials.

Monitoring for efficacy and toxicity is also essential for the evaluation of drugs and their preparations and this is the subject of an excellent chapter by the editors of the book, Dr Richards and Professor Lawson. They draw attention to the under-utilization of pharmacists' knowledge and skill and point out that, with additional training, the latter can realize their full potential in the field of drug monitoring. Proposals are made for such training and for the role of pharmacists in the subject.

Since potent drugs are bound to affect body systems other than those on which their action is desired, adverse reactions are inevitable and are part of the price society has to pay for pharmacological advances. Professor Lawson discusses adverse drug reactions in considerable detail including methods of studying and recording them. This chapter will be especially useful to clinical pharmacists.

I have been interested in intravenous additive services since visiting several European units during the WHO Fellowship in 1961 and others in the United States in the early 1960s. I was also a member of the Breckenridge Committee along with Dr Smail and Mr Marshall and am thus aware of their valuable contributions to its deliberations. Their chapter is an excellent review of the subject.

A welcome trend is the increasing involvement of pharmacists in both enteral and parenteral nutrition. The subject is discussed in considerable detail by Dr Farwell who stresses the need for a team approach.

It is appropriate that Mr Bell, a pharmacist, and Dr Horton, a medical physicist, have together written the chapter on Radiopharmacy, since this is another subject which requires close collaboration between professional colleagues. They describe the uses and handling of radio-pharmaceuticals.

Pharmacies have acted as sources of drug information for many years. The Extra Pharmacopoeia (Martindale), for example, developed out of notes kept by William Martindale for that purpose when he was Chief Pharmacist of University College Hospital (1868–73). The vast increase in the number and variety of medicinal preparations in the past three decades or so has emphasized the need for information services whilst the introduction of new techniques such as microfiche and computers has facilitated their provision.

Hospital pharmacy was organized into larger units following the implementation of the recommendations of the Noel Hall Report and the National Health Service reorganization and this has enabled drug information services to be rationalized into units of convenient size according to local circumstances. The development and organization of such services is described by Mrs McCabe and Dr Richards.

A chapter by Messrs Barrett, Willson and Baker describes the development and decline of hospital pharmacopoeias, some of which are of considerable historical interest, and their replacement by a new type of hospital formulary. They also give the results of eight years experience in the development of a British Hospital Formulary system.

The final chapter on purchasing and control of hospital medicines is by my friend and former colleague Mr Graham Calder. No one is

better qualified than he for this task as he was the pioneer of the 'Aberdeen System' which is known throughout the English-speaking world and beyond. Mr Calder describes the various systems in use in this country and abroad with their advantages and disadvantages. He also discusses the legal aspects of the purchase, storage and distribution of medicines and related products and the roles of the persons involved, together with their training needs.

Most of the chapters of the book have useful lists of additional reading matter. It can be confidently recommended to pharmacy students and practising pharmacists.

T.D. Whittet
C.B.E., B.Sc., Ph.D., F.P.S.
Formerly Chief Pharmacist to the Department of Health and Social Security, London

Preface

In many hospitals, pharmacists have confined their interests largely to purchasing drugs for the hospital and rendering those which are prescribed available to the patient or sometimes only to the ward in which the patient resides. This preoccupation with the logistics of drug therapy has eventually led pharmacists in many hospitals into becoming the main group of professionals responsible for ordering all major consumable materials for patient care, i.e. syringes, dressings, IV infusion sets, surgical instruments etc. While this task may require careful attention to detail it hardly requires the high professional skills acquired by our pharmacy graduates over their years of undergraduate training and pre-registration study. It is therefore heartening that the profession of pharmacy is at last becoming aware of the unfulfilled needs of prescribers in hospital – need for considerable expertise in pharmacology and clinical pharmacy which should be and indeed often are part of the hospital pharmacist's stock in trade but which all too readily are allowed to atrophy under the unrelenting pressure of day to day hospital routine. Several universities appreciate this problem and are now encouraging final year degree students in Pharmacy to attend courses in Clinical Pharmacy – indeed some have provided higher degree courses in this topic for selected individuals.

The present book is designed to focus the attention of pharmacists on the many factors which are relevant to treatment with modern medicines. The opening chapter considers in greater detail than heretofore the too-long ignored aspect of the clinical significance which formulation has on the performance of a medicine. That is the clinical effects and interactions of formulation adjuvants as well as the effect of formulation on the bioavailability of the active principal. This is followed by an up-to-date account of the means whereby the quality of the prescribed product is ensured. The book then progresses

to a consideration of the practical usefulness of various pharmacokinetic measurements in the control of drug therapy. Thereafter, the many factors which can account for the wide differences in response to drug treatment are considered. Such discussions are based on the assumption that the patient is consuming the prescribed medications as directed by his physician. This may, however, be far from true - a habit which sometimes may render prescribed therapy ineffective and often times may render it less toxic than would otherwise have been the case! This problem of compliance is intimately involved in the patient's relationship with his medical attendant and his comprehension both of the need for treatment and the consequences of not adhering to prescribed schedules. These aspects of compliance are considered in detail in a chapter which includes various new ideas on the role of the pharmacist in educating the patient about drug treatment.

Clinical trials of formulated medicines are discussed from particularly pharmaceutical aspects and the emerging role of the pharmacist in monitoring drug treatment from the stand point of efficacy and toxicity is then considered. This latter role involves a discussion of areas of patient-orientated pharmacy practice and provides practical suggestions for teaching and practice to enable the pharmacist to obtain confidence and competence for such developing situations.

Multiple drug treatment is virtually the rule in hospital medicine. Thus the risks of adverse drug effects and drug interactions in this environment are often large. In a separate chapter the importance of drug interactions are emphasized, particularly those of a pharmacodynamic rather than a pharmacokinetic type; the latter with a few notable exceptions being of academic rather than immediate practical value.

Pharmacy-based intravenous additive services provide an important contribution to patient care in many hospitals and the factors involved in providing these services are considered. In addition, the contribution of the pharmacist in nutrition, especially the highly specialized area of total parenteral nutrition is discussed.

Radiopharmacy is another specialized field which is considered in detail and in this developing area co-operation between the pharmacist and the physicist has resulted in a safe and efficient service to the patient.

Substantial concern over the increasing cost of drugs is evident from governmental sources worldwide. Many factors come together to influence hospital prescribing but rarely is cost the pre-eminent or even an important consideration. This is unfortunate since, as a result

of increasing constraints on the pharmaceutical industry both in the UK and abroad, we have recently experienced a rash of 'me-too' type drugs which have little to distinguish one from the other except such clinically irrelevant matters as cost. Thus there is a need for better systems for providing prescribers with information about many more facets of drug therapy than are available readily at the present time. The role of the pharmacist in providing such information is emphasized and the sources of information available to them are described in detail.

The production of hospital formularies for specific hospitals, or district drug guides for groups of hospitals, with a view to encouraging more rational drug therapy is both a topical and controversial topic. This area of practice is placed in context and valuable first-hand experiences are shared.

The concluding chapter provides a description and assessment of the important area of the purchase, supply and control of hospital medicines thus completing a coverage of pharmaceutical topics aimed at not only bringing the reader up to date with a range of modern pharmaceutical practice but also in certain instances at pointing the way to expected future developments in the field.

Glasgow, 1981

David H. Lawson
R. Michael E. Richards

Contents

1

The Clinical Relevance of the Formulation of Medicines

A. T. FLORENCE and E. G. SALOLE

Textbooks of pharmacology or of clinical pharmacology often neglect the fact that drugs are rarely used as such but are administered to patients as formulated medicines. Ideally this should not influence the nature or quality of the action of the drug, indeed in many cases formulation does not affect drug activity, but the nature of the formulation exercise dictates that sometimes there will be a need to take cognisance of the formulation. It is obvious, when considering specialized (e.g. sustained-release) medications, that the formulation has a direct influence on the time-course of drug action; it is less clear in the common case of formulations which are intended only to be a means of administering drugs to the body in convenient form. There is a growing awareness of the need to be cautious in interpreting drug trials where formulations are inadequately characterized. There should also be an awareness that adverse reactions to medicines might sometimes be due to the 'physiologically inert' excipients present in the formulation. This chapter is not an account of formulation techniques; rather it is an attempt to place formulation in clinical perspective, firstly by discussing the role of formulation in producing medication for different routes of administration, and secondly by drawing attention to the role of the formulation in drug activity and adverse drug reactions. A treatment of this subject of necessity brings into focus the problem of generic inequivalence and the role of extemporaneous dispensing of untested formulae, topics which are interlinked.

Modern formulation techniques are concerned not only with manipulation of inert ingredients to provide suitable vehicles for the drug substance, but also with modification of the drug itself to produce, for example, poorly soluble salts to minimize an obnoxious taste or to prolong drug action. For instance the ester derivatives of erythromycin have been designed to increase absorption by

protecting the antibiotic from breakdown in the gastrointestinal tract. The neglect of the salt, ester or other form of the drug can have a significant effect as the forms may not be bioequivalent, and dosage calculations can be confused if the appropriate molecular weights are not considered. Adequate information rarely appears on product labels and thus the presence of 'inert' ingredients such as binders, fillers, preservatives, flavours, colours, antioxidants and other vehicle components (e.g. non-aqueous solvents and surfactants) may be unrecorded. Information on formulation is the province of the pharmacist and it is vital that he or she transmits information on product formulation to the physician when it is significant; too little information is readily available on this subject, nevertheless the pharmacist must assiduously seek it out. He or she must also be aware of the possible consequences of misuse of formulated medicines, such as the crushing of slow-release or enteric-coated tablets, the injection of oral suspensions, the dilution of injections into infusion fluids and the intra-arterial use of injections containing preservatives. This chapter intends to do no more than highlight certain problems that have been reported in the literature and alert users to potential problems. As with all subjects dealt with in this volume, any problems concerning the use of formulations must be placed in proper perspective; it is, none the less, the obscure reactions in the minority of patients which place the greatest strains on diagnosis and corrective action. Methods of evaluation of dosage forms have to be applied more frequently in the pharmacy to determine the performance characteristics of products being used in the hospital or intended for clinical trial. Dissolution tests of solid dose forms and dilution characteristics of injectable preparations as well as more ambitious involvement with bioavailability studies are part of the topic under consideration.

1.1 Formulations for the oral route

Oral therapy is, for many drugs, the preferred route of administration, the choice of solid or liquid dosage forms depending on not only the nature of the drug substance and dose volume but also the patient, an aspect of particular importance in the treatment of young children and geriatric patients. This common route of drug administration though convenient and providing a large margin of safety does not necessarily ensure reliable absorption, even of drugs presented as solutions in an attempt to avoid the vagaries of solid form disintegration and dissolution. A drug formulated as a solution in,

for example, a non-aqueous solvent may precipitate on dilution by the contents of the stomach; the drug would then have to redissolve before being absorbed, the rate of dissolution depending on factors including the particle size of the precipitated material and its solubility. Similar discrepancies in the bioavailability of solutions might occur when aqueous solutions formulated at a given pH for maximum stability and solubility admix with the gastric contents.

Although there is now some evidence that particulate matter can be absorbed from the gastro-intestinal tract, drug absorption is generally preceded by solution of the drug. If a tablet or hard-shell gelatin capsule is used the first stage in the absorption process is the disintegration of the dosage form (Fig. 1.1). Consideration of particle

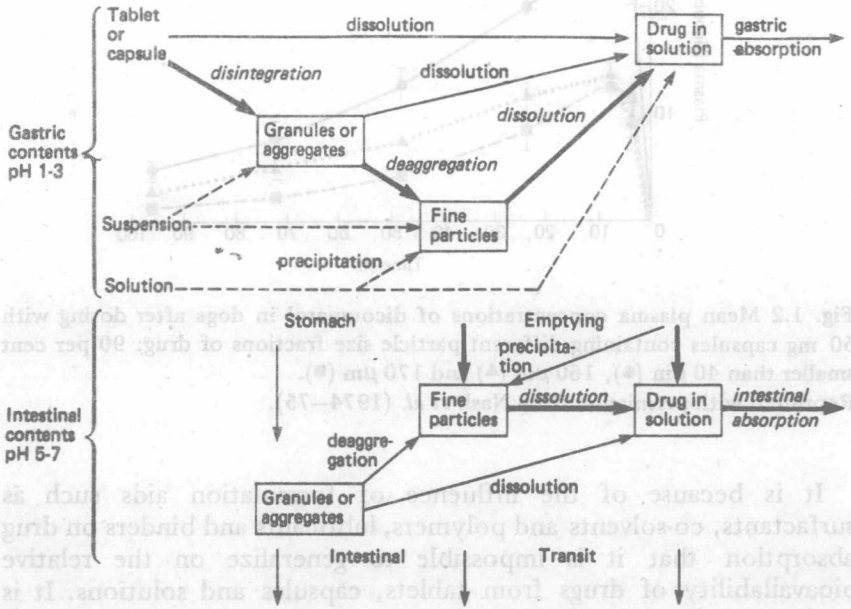

Fig. 1.1 The processes involved in the absorption of a drug from a formulation administered orally: heavy arrows indicate the most important dissolution pathways, thin continuous arrows the secondary pathways (in most cases inconsequential) and dashed arrows indicate that the drug has been administered in the form shown.
Reprinted with permission from Benet (1973).

size is especially important in clinical trial materials or when a medication, such as a suspension, is prepared extemporaneously in