Topical Skin Therapeutics

M. K. Polano

Topical Skin Therapeutics

M. K. Polano
Emeritus Professor and Chairman, Department of Dermatology, Leiden University Medical Centre, The Netherlands; formerly Head of the Dermatological Department, Municipal Hospital, The Hague, The Netherlands

With the editorial assistance of

P. J. August
Consultant Dermatologist, The Skin Hospital, Manchester, UK

FOREWORD BY

Arthur Rook MA, MD, FRCP
Consultant Dermatologist, Addenbrooke's Hospital, Cambridge, UK

CHURCHILL LIVINGSTONE
EDINBURGH LONDON MELBOURNE AND NEW YORK 1984

CHURCHILL LIVINGSTONE
Medical Division of Longman Group Limited

Distributed in the United States of America by
Churchill Livingstone Inc., 1560 Broadway, New York,
N.Y. 10036, and by associated companies, branches and
representatives throughout the world.

First published 1984

ISBN 0 443 01914 2

British Library Cataloguing in Publication Data
Polano, M. K.
Topical skin therapeutics.
1. Skin—Diseases—Chemotherapy
2. Dermatopharmacology
I. Title
616.5'061 RL110

Library of Congress Cataloging in Publication Data
Polano, M. K. (Machiel K.)
Topical skin therapeutics.

Bibliography: p.
1. Dermatologic agents. 2. Dermatopharmacology.
I. August, P. J. II. Title.
RL801.P65 1984 615'.778 84–3210

Printed in Singapore by Selector Printing Co (Pte) Ltd

Foreword

The range of topical applications prescribed by many dermatologists is now often more limited than it was 30 years ago. This is in part a result of the ready availability of widely advertised proprietary preparations, particularly of those containing corticosteroids alone or in combination with antibiotics. It cannot be denied that the development of these pharmacologically active substances is the most important advance in the history of the therapeutics of the skin. Nor can it be denied however, that they are frequently prescribed in the treatment of conditions in which, at best they cannot be of any benefit, and which at worst they may aggravate insidiously or acutely and spectacularly.

Professor Polano of Leiden has long been interested in all aspects of topical therapy. In his very practical book, based on his wide experience and a critical review of the international literature, the criteria for selecting the appropriate active ingredients and the influence on these of the vehicle in which they are dispensed, are discussed. The most effective management of skin disorders often depends on the use of a judicious combination of the new and the old.

All over the world the rising cost of medical care is a growing problem. There are many conditions which can be treated as effectively, or even more effectively, with traditional remedies than with the latest product of pharmaceutical research. In many chronic eczemas, for example, tar pastes are invaluable and dithranol (anthralin) is often to be preferred to corticosteroids in psoriasis. The choice of the appropriate agent in the appropriate vehicle is an art and science which is sometimes neglected. The ideal is to prescribe for each patient the most effective treatment regardless of cost. Fortunately the best treatment is sometimes the cheapest. On the other hand there are circumstances in which the most expensive is the most cost-effective.

Professor Polano emphasises the importance, not only of selecting the right substance and the right vehicle, but also of ensuring that the patient knows how and when to apply what is given and that the quantity prescribed is suitable for the area to be covered—too often little attention is paid to prescribing as precisely as possible the correct quantity. Much

money is wasted by prescribing excess amounts and on the other hand prescribing too little inconveniences the patient and treatment is interrupted.

The use of this book should encourage greater flexibility of prescribing for it contains much practical information not easily accessible elsewhere.

Addenbrooke's Hospital,
Cambridge, 1984

Arthur Rook

Preface

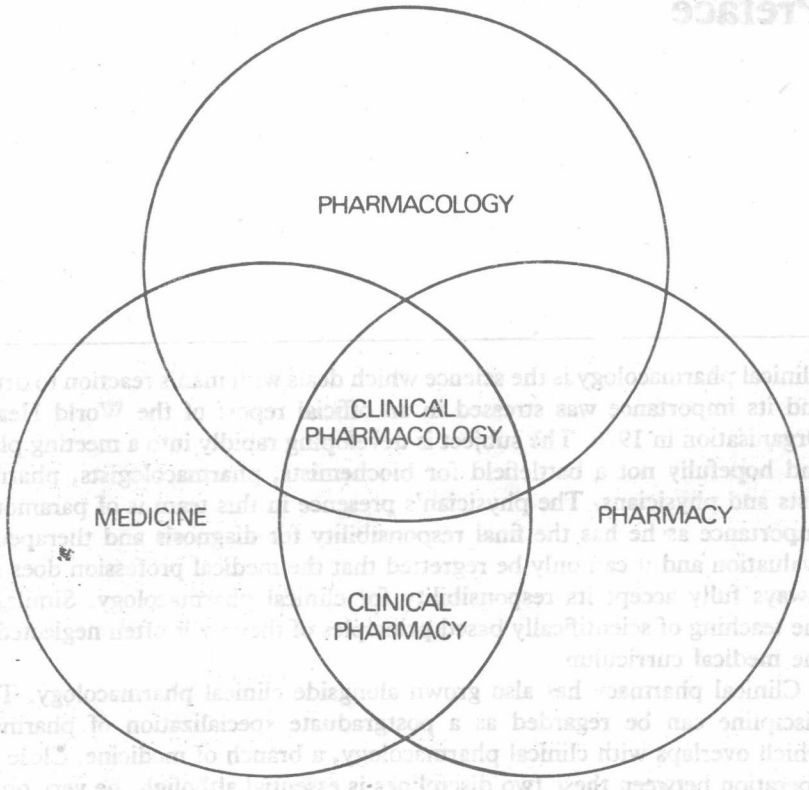
Clinical pharmacology is the science which deals with man's reaction to drugs and its importance was stressed in an official report of the World Health Organisation in 1970. The subject is developing rapidly into a meeting place and hopefully not a battlefield for biochemists, pharmacologists, pharmacists and physicians. The physician's presence in this team is of paramount importance as he has the final responsibility for diagnosis and therapeutic evaluation and it can only be regretted that the medical profession does not always fully accept its responsibility for clinical pharmacology. Similarly, the teaching of scientifically based principles of therapy is often neglected in the medical curriculum.

Clinical pharmacy has also grown alongside clinical pharmacology. This discipline can be regarded as a postgraduate specialization of pharmacy which overlaps with clinical pharmacology, a branch of medicine. Close co-operation between these two disciplines is essential although the very opposite occurs at times. The clinical pharmacist can give invaluable information to the clinical pharmacologist and other clinicians who make the final judgement about the efficacy of the prescription and the response to it.

This implies that the closest possible collaboration between pharmacists and dermatologists is indispensable. The pharmacist should regularly inform the dermatologist of the possibilities inherent in new active drugs and vehicles, in return for information on the results obtained in clinical practice. Clinical pharmacology of the skin, particularly the topical aspects, is so complex that it can not be covered adequately by the general clinical pharmacologist alone. It is necessary for dermatologists to play a significant part in the clinical topical pharmacology of the skin. This is offered as an alibi for the publication of a book on this subject.

In 1952 I wrote a book *Skin Therapeutics, Prescription and Preparation*, on Materia Medica of the skin, which was kindly received. As the useful life of a book on a rapidly progressing science is short, I was often asked for a second edition, but never found time for it. So much progress has now, fortunately, been made in this field that not a second edition, but a completely rewritten book with a new name has been undertaken.

Despite a continuing decline, already evident in 1952, in the popularity of



extempore prescriptions in favour of proprietary medicines, it is still essential for the clinician to remain fully aware of what is being prescribed and why. He should not only be acquainted with the clinical pharmacology of the specific drugs, but also with the characteristics of the delivery systems such as the vehicles and pharmaceutical aids. The recent development of biopharmacy and pharmacokinetics has made this even more necessary.

The aim of this book is to build two bridges, one between pharmacologists, pharmacists and dermatologists, and the other between the students of these disciplines internationally. It is notable that international differences in the field of use and nomenclature of drugs and pharmacopoeial prescriptions are far greater than in the field of pathology and diagnosis.

The volume starts with general remarks on the basic considerations underlying the prescription and preparation of drugs intended for topical use. Chapters then follow on the characteristics of the basic substances for the vehicles and the way in which they are formulated. Subsequently the properties of the active substances that are applied in these vehicles are discussed in detail. In spite of the prominence since 1952 of the glucocorticosteroids and the remarkable progress in the field of topical antibiotics, antifungal agents and antiparasitic drugs, adequate emphasis is given to the

classical drugs that made dermato-therapy possible before 1952, coincidentally the date of publication of my first book on skin therapeutics.

A chapter on dosage in topical dermatotherapy, an often neglected subject, follows. Next comes a discussion of the trial methods that are designed for the evaluation of the toxicity of drugs in the widest sense, and for the estimation of the penetration of drugs into and through the skin. The theory and practice of clinical trials are discussed. In 1961 Harvey Blank had already emphasized that this discipline is an indispensable aid to our judgement on the merits and demerits of new drugs. Unfortunately drug trials are not always well designed or are misinterpreted in promotional literature.

The formulary was adapted from that prepared by Professor D. Suurmond for dermatologists in training in the dermatology department of the Leiden University Medical Centre and exemplifies how the principles of the previous chapters may be put into practice. The author thanks his successor for his permission to include this.

As generic, rather than proprietary names are preferred, the former have been listed, followed by the proprietary name appropriate in the UK, the USA and where necessary, a few continental countries. The general index enables the reader to find the generic name of proprietary drugs. Another table will clarify the differences between the nomenclature and formulation of the British Pharmacopoeia, the Pharmaceutical Codex, the British National Formulary, the US Pharmacopoeia, the US National Formulary, the Pharmacopoeia Europeana and the Formulary of the Netherlands' Apothecaries.

The author has not aimed at a comprehensive reyiew of this vast subject. A personal opinion has been given deliberately. This would seem to be of more use to the reader than an impersonal reference work on a very extensive subject.

The book is intended for dermatologists in training, for dermatologists committed to the principles and possibilities of topical therapy, for clinical pharmacologists and pharmacists interested in the skin and for all those involved in the design and the development of new drugs for the skin.

An author is, of course, indebted to so many persons that it is an invidious task to choose those who merit special mention. Aware of this, I express my thanks to all those who co-operated with me in the dermatological departments of the municipal hospital in the Hague and of the Leiden University Medical Centre; senior dermatologists, registrars, students, nurses, laboratory workers, they all will find opinions expressed which are the results of our common work. I am grateful to my colleagues of the Leiden University for discussions which have contributed to the final shape of the opinions expressed here, especially to Professors H. de Jonge (Department of Medical Statistics), D D. Breimer and E.L. Noach, (Department of Pharmacology) and J. Polderman, (Department of Pharmaceutical Technology and Pharmaceutics). Dr W.A. Herrman, dermatologist in The Hague, Netherlands, has read the whole manuscript critically. Thanks are also due

to Mrs P.J. Spuyman, Mrs Jill McCann and Mrs W. Jones who typed and retyped the manuscript with patience and perseverance.

I highly appreciate the willingness of Dr Arthur Rook, to whom every dermatologist is indebted for his important contributions to dermatological literature, to write an introduction to this book.

It is a bold, if not foolhardy endeavour to write a book in a language which is not one's own. I certainly would have failed without the help of Dr P.J. August, Consultant Dermatologist to the Skin Hospital of the University of Manchester School of Medicine, who was willing to undertake the linguistic editing of the book and to compile the index. He did, however, much more; he contributed a number of conceptual improvements and permitted the inclusion of prescriptions that had proven themselves particularly useful in his practice and references to unpublished results of his personal research. I esteem his unselfish help immensely.

Finally I have to thank Churchill Livingstone for their friendly cooperation and encouragement during the preparation of this book.

It is with hesitation if not trepidation that this book is offered; criticisms will be highly appreciated by the author.

1984 M.K.P.

REFERENCES

Blank H 1961 Clinical trials, a scientific discipline. J. Invest Dermatol 37: 225–240

Polano M K 1952 Skin therapeutics (Materia Medica dermatologica). Elsevier, Amsterdam

Explanatory notes

Glossary of abbreviations

AMADE	American Medical Association Drug Evaluations 1983
BAN	British Approved Names 1981
BP	British Pharmacopoeia 1980
BNF	British National Formulary 3 1982
EP	Extra Pharmacopoeia (Martindale) 1982
FNA	Formularium van de Nederlandse Apothekers (Formulary of the Netherlands' Apothecaries)
NF	National Formulary (included in the USP)
PC	Pharmaceutical Codex XI (UK) 1979
Ph Eur	European Pharmacopoeia 2nd edn 1980
Ph Int	Pharmacopoeia Internationalis 3rd edn (WHO) 1981
USAN	United States Approved Names 1983
USP	United States Pharmacopoiea XX 1980
USP DI	United States Pharmacopoeia Dispensing Information

Note on references

The lists of 'References' after each section cover the literature up to 1 March 1982 and are discussed in the text. 'Additional references' deal with the literature subsequent to 1 March 1982. In the section 'Suggested further reading' are listed books and monographs of special interest. They may or may not be considered in the text.

Contents

1

General considerations

CLINICAL PHARMACOLOGY OF THE SKIN AND TOPICAL APPLICATIONS

The advent of effective drugs has changed the way in which these are made available and prescribed. Formerly a physician chose specific drugs which he assumed to be beneficial in the disease in question and required the pharmacist to mix them in specified proportions with carrier substances called 'vehicles'. In dermatology, instructions were conveyed to the pharmacist by a prescription. Thus the symbol R/ at the beginning of the prescription stands for recipe, i.e., take the specified substances. Sometimes the prescription would specify the manner in which the substances had to be mixed, otherwise it was understood that the pharmacist would prepare the prescriptions *lege artis*; according to the rules of his art. The basic principles of prescribing topical applications are unfortunately often neglected in the medical curriculum. Application of these principles to skin therapeutics will be discussed in Chapter 3.

In the last 50 years the pharmaceutical industry has not only developed new drugs with outstanding topical activity, but has also produced these ready for use in vehicles. A few decades ago little attention was paid to these vehicles. Often soft paraffin or a cosmetically acceptable cream was used. The development of biopharmacy and investigations into the bioavailability of drugs has made considerable changes in this practice.

A frequently used method in clinical pharmacology estimates blood levels of a drug in order to ascertain what proportion reaches the circulation. An equivalent for topical therapy is the measurement of the content of suction blisters, which indicates the concentration in the interstitial fluid (Herfst & Van Rees, 1978). Currently, active drugs are often incorporated in tailor-made delivery systems using vehicles chosen as carefully as the drug for which they are intended.

Since 1952, when the first edition of this work appeared, a further undeniable shift in prescribing habits towards proprietary drugs has become evident. For a time there seemed to be rivalry between prescription drugs and proprietary preparations. The author used to recommend that wherever

possible a prescription should be given for an *ex tempore* formulation from the pharmacy, in preference to a proprietary preparation. As the costs of labour in the pharmacy have risen steeply and the willingness of pharmacists to compound topical preparations has declined, this view can no longer be sustained. It is self evident that the patient should have the best. Detailed knowledge of clinical pharmacology, clinical pharmacy *and* costs is necessary in order to achieve the best value. It should not be beneath the dignity of a physician to be cost conscious in the interests of patients and the community—it is regrettable that Zelneck and Gagon (1974) had to point out the lack of interest shown by the medical profession in this aspect of pharmacotherapy; it is a good sign that Arndt (1978) gives explicit attention to this subject in his manual of therapeutics. The BNF also gives information on prices.

A frequently quoted advantage of proprietary preparations is that they are prepared in batches of uniform quality, bio-availability and drug content. However, formulations prescribed and dispensed competently are perfectly satisfactory, though it must be admitted that there may be differences in pharmacokinetics between apparently identical products from different manufacturers or pharmacies. A notable disadvantage of proprietary preparations is that the exact formula is not apparent to the dermatologist. As a rule only the active substance is specified and the composition of the vehicle, which may contain irritants and sensitizers, is at best mentioned in very small print on the package insert. It is only practicable for the dermatologist to obtain the formulae from the manufacturer if sensitization is suspected.

It is often argued that prescriptions made in a pharmacy are cheaper than those available commercially, but this is not necessarily so. It is cheaper to prescribe a proprietary antibiotic-corticosteroid combination than to ask the pharmacist to add an antibiotic to a corticosteroid cream. On the other hand it is more economical to add those corticosteroids available in bulk to one of the vehicles described in Chapter 3 than to use a proprietary application.

The dermatologist who prescribes a proprietary preparation, old or new, must be acquainted with the characteristics of all its components. He must also be familiar with the methodology of the clinical trials to assess the claims made for a new drug, and to decide if 'new' is really 'better', or if the new drug is merely a 'me too'. There is otherwise a risk that prescribing habits will degenerate into juggling with the latest proprietary drugs to be advertised.

The importance of knowing the chemical composition of the drug used in dermatology has already been mentioned. Few can be expected to memorize full chemical names such as 11β 17α 21-trihydroxy-4-pregnene-3, 20-dione; the name 'hydrocortisone' is easier and is often called the generic name. Laurence and Bennett (1980) point out that this is a misnomer. A generic name points to a family or genus of drugs such as benzodiazepines, sulphonamides, corticosteroids. It is more correct to use the term 'non-proprietary name'. However, as the term generic name is currently used for the same

purpose and is shorter, both terms will be used synonymously in this book.

A proprietary name such as Efcortelan® is the property of a pharmaceutical firm and remains so when the substance is no longer protected by a patent. Proprietary names are often shorter and more euphonious than generic names and may point to a presumed therapeutic activity which may be unjustifiably promotional. A drug prescribed under its generic name must be dispensed in the most economical way. When the proprietary name is used on the prescription, this specific trademark must be dispensed irrespective of relative cost. Although it is usually desirable to think about drugs in generic rather than trade names, an exceptional situation sometimes occurs in dermatological prescribing. Theoretically, all prescriptions of 1% hydrocortisone ointment should be identical but in fact the base used will be different depending on the manufacturer. It is possible to avoid sensitizers and to vary the physical appearance of the formulation given to the patient by using the product of specified manufacturers, or by using a base of one's choice as an extempore prescription.

When a substance is recognized as a potential drug, it has to be given a non-proprietary name. Three registration offices exist for such names: an office of the WHO which recommends an International Non-proprietary Name (INN), the British Pharmacopoeia Commission, which registers the British Approved Name (BAN) and the United States Approved Names Council for the United States Approved Name (USAN).

In the British Pharmacopoeia (BP) the BAN name followed by the chemical formula is used as the heading for the monographs. In the United States Pharmacopoeia (USP) the chemical name is added to the USAN name. The names issued by these three agencies are very similar and generally only differ by the suffix e.g. Chloroquine BAN – Chloroquinum INN. In this book the BAN will be used, but where confusion might arise, the INN and/or USAN will also be mentioned.

In pharmacy prescriptions one may use a formula from an official formulary, e.g. calamine lotion (BP). This will be an application of well tried composition. However, there is a disadvantage that the prescriber may not be aware of all the constituents. This problem is avoided if the prescription is written out in full, and the percentages of active drugs may be more precisely adapted to the needs of the patient. On the other hand, overdiversification in prescribing habits is pointless.

The original basis of therapeutics, including that of the skin, was largely empirical. 'Empirical' is often used in a derogatory sense, meaning a haphazard and unmethodical collection of observations. Although many therapies now have a firm theoretical basis, the final evaluation of drugs has nevertheless still to be conducted empirically.

Topical applications must also be carefully screened for undesired side-effects. This includes acute and chronic toxicity, local as well as systemic effects, sensitization index, phototoxicity and photosensitization (Ch. 7). Some traditional treatments used for many years have been discarded because

of proven systemic toxicity or an unacceptable sensitization index or a lack of demonstrable therapeutic activity. This was the case with ammoniated mercury (Young, 1960). It was rightly discarded from the USP, 19th edition, but again inexplicably admitted to the 20th edition and is also still mentioned in the PC and FNA.

Accurate assessment of the skin sensitization potential of a new drug is very difficult, so it often takes some years before this property becomes apparent. A classical example of an unacceptable risk to benefit ratio is the high sensitization index of topical antihistamines, especially promethazine hydrochloride (phenergan®), which was only noticed after years of use. This is, nevertheless, still marketed as a cream. Topical applications containing penicillin and most of the sulphonamides, have been discarded for the same reason.

CHANGING TRENDS IN OFFICIAL FORMULARIES

Originally the prescriber was limited to concoctions of vegetable and other substances which he often dispensed personally. The directions for prescriptions were handed from teacher to pupil, sometimes as a secret. Gradually, prescriptions were compiled into pharmacopoeias of only local or regional importance. The first pharmacopoeia in the Netherlands, the Pharmacopoeia Amstelodamensis, was edited in 1636 by Nicholas Tulp, immortalized in Rembrandt's famous painting of the anatomy lesson. In the 19th century, national pharmacopoeias replaced the regional versions. The Swiss (1775) and Batavia (Netherlands) (1805), pharmacopoeias are among the earliest. It is interesting to note that the initiative for these pharmacopoeias generally came from the medical profession. In due course pharmacists were admitted to the pharmacopoeia boards and legal status was obtained. It is beyond the scope of this book to describe or follow the evolution of official prescription books in all countries, although their history provides an interesting reflection of the interaction between the pharmaceutical and medical professions. Originally, the pharmacist's skill and experience were applied only to ensure that the drugs chosen by the physician were of good standardized quality and delivered in suitable vehicles. In retrospect a large proportion of the official drugs formerly described in pharmacopoeias had at best a placebo effect.

In 1858 the first British Pharmacopoeia (BP) was published by direction of the General Medical Council, describing in monographs the identity, strength and standard of purity of a selection of current drugs and a number of compound preparations. In 1903–1907 the council of the Pharmaceutical Society of Great Britain prepared a Codex (BPC) intended for those prescribing and dispensing drugs. This Codex reprinted the monographs of the pharmacopoeia and added information on therapeutics and side-effects. It also contained a number of new drugs not yet mentioned in the pharma-

copoeia and a considerable number of compound prescriptions were described, including directions for their compounding. In 1979 and 1980 there were significant developments. The Pharmacopoeia was extended and published in two volumes, one with monographs, a number of which were formerly published in the BPC, and the other with formulations for compound preparations. In connection with this development, the British Pharmacopoeia Codex (BPC) changed into 'an encyclopaedia of drug information of interest to the pharmacist'. It includes the monographs of the pharmacopoeia and a number of extra compound preparations. Finally it contains condensed medical information on diseases.

The British National Formulary (BNF) has been published at regular intervals since 1946. It should not be confused with the National Formulary (NF) which has appeared in the USA since 1899. In 1948 the BNF was aimed primarily at simplicity and uniformity in the prescriptions of the familiar compound mixtures, current at that time. This rationalization undoubtedly saves labour and consequently money.

The BNF also contains an excellent selection of prescriptions and proprietary drugs for skin diseases. Pertinent information is given on pharmaceutical characteristics, side effects, incompatibilities, medical use and other important topics. From 1981 onwards new editions with a wider scope appear regularly. These contain not only 'the products that have the confidence of the committee' as in the previous editions, but also a comprehensive list of proprietary drugs. The 3rd edition (1982) lists the skin preparations in 12 different categories. In each category, the preparations are listed in the order of their usefulness in the opinion of the editors. Those preparations that are less suitable appear in small print. One hopes that this arrangement will give the general practitioner adequate guidance through the jungle of proprietary preparations. An advantage is that new popular proprietary preparations are listed in an official source. It seems questionable on the other hand that the practitioner will receive much guidance from such abundance. The BNF editions since 1981 give information on the price of the drugs described, but unfortunately do not allow for the cost of dispensing. The section on quantities of preparations for the skin would be improved by stating the frequency and period of use for which the quantities are appropriate.

A most useful contribution to pharmaceutical information is the Extra Pharmacopoeia (EP) published for the first time by Martindale in 1878 and regularly updated since then. It contains much of the information available in the BP and BPC and also the specifications of proprietary drugs, including their proprietary and generic names which are cross indexed. There is a wide range of international pharmaceutical information including references to the literature on the uses and toxicity of drugs.

Another publication is MIMS, the monthly index of medical specialities, circulated free to all doctors in the UK. It contains an up to date list of all proprietary preparations, including the cost, manufacturer, and limited information about appropriate use.