Edited by
J. D. Williams and A. M. Geddes

CHEMOTHERAPY

Volume 5

Penicillins and Cephalosporins

CHEMOTHERAPY

Volume 5
Penicillins and Cephalosporins

Edited by
J.D. Williams
The London Hospital Medical College
London, U.K.

and
A.M. Geddes
East Birmingham Hospital
Birmingham, U.K.

Plenum Press · New York and London

Library of Congress Cataloging in Publication Data

International Congress of Chemotherapy, 9th, London, 1975.
Penicillins and cephalosporins.

(Chemotherapy; v. 5)
1. Penicillin—Congresses. 2. Cephalosporin—Congresses. I. Williams, John David, M.D. II. Geddes, Alexander McIntosh. III. Title. IV. Series.
RM260.2.C45 vol. 5 [RM666.P35] 615'.58s [615'.329'23] 76-1943
ISBN 0-306-38225-3

Proceedings of the Ninth International Congress of Chemotherapy held in London, July, 1975 will be published in eight volumes, of which this is volume five.

A Division of Plenum Publishing Corporation
227 West 17th Street, New York, N.Y. 10011

United Kingdom edition published by Plenum Press, London
A Division of Plenum Publishing Company, Ltd.
Davis House (4th Floor), 8 Scrubs Lane, Harlesden, London, MW10 6SE, England

Printed in the United States of America

CHEMOTHERAPY

Proceedings of the
9th International Congress of Chemotherapy
held in London, July, 1975

Preface

The International Society of Chemotherapy meets every two years to review progress in chemotherapy of infections and of malignant disease. Each meeting gets larger to encompass the extension of chemotherapy into new areas. In some instances, expansion has been rapid, for example in cephalosporins, penicillins and combination chemotherapy of cancer - in others slow, as in the field of parasitology. New problems of resistance and untoward effects arise; reduction of host toxicity without loss of antitumour activity by new substances occupies wide attention. The improved results with cancer chemotherapy, especially in leukaemias, are leading to a greater prevalence of severe infection in patients so treated, pharmacokinetics of drugs in normal and diseased subjects is receiving increasing attention along with related problems of bioavailability and interactions between drugs. Meanwhile the attack on some of the major bacterial infections, such as gonorrhoea and tuberculosis, which were among the first infections to feel the impact of chemotherapy, still continue to be major world problems and are now under attack with new agents and new methods.

From this wide field and the 1,000 papers read at the Congress we have produced Proceedings which reflect the variety and vigour of research in this important field of medicine. It was not possible to include all of the papers presented at the Congress but we have attempted to include most aspects of current progress in chemotherapy.

We thank the authors of these communications for their cooperation in enabling the Proceedings to be available at the earliest possible date. The method of preparation does not allow for uniformity of typefaces and presentation of the material and we hope that the blemishes of language and typographical errors do not detract from the understanding of the reader and the importance of the Proceedings.

K. HELLMANN, Imperial Cancer Research Fund
A. M. GEDDES, East Birmingham Hospital
J. D. WILLIAMS, The London Hospital Medical College

Contents

THE BETA LACTAM ANTIBIOTICS - PENICILLINS AND CEPHALOSPORINS

G.T. Stewart

Department of Community Medicine

University of Glasgow. U.K.

INTRODUCTION

There are five criteria by which maintenance and development of activity in this leading group of antibiotics can be assessed:

1) Width of antimicrobial spectrum
2) Action on penicillinase-forming bacteria
3) Pharmacological improvements
4) Non-toxicity
5) Diminution of allergic responses

1) Width of Spectrum

It has to be remembered that earlier natural penicillins like penicillin G and penicillin N (as Abraham reminds us) possess considerable intrinsic activity against certain gram-negative bacilli, especially of the coli-typhoid group. Ampicillin and its homologues have extended this activity to a wider range of organisms in the same group as well as to haemophilus, to Proteus mirabilis, and to various streptococci. There is evidence of increasing resistance in hospital and non-hospital strains of E.coli to ampicillin, less so to its derivatives and homologues, though precise comparisons are difficult in the face of differences in local patterns of use, abuse and recording of data. The work of our colleagues in the Scandinavian countries on Bacampicillin and Mecillinam is therefore of special interest. Carbenicillin, with relatively weak activity against Pseudomonas and Proteus spp. is still useful though also threatened by resistant organisms. Rodriguez suggests a novel use for it against ampicillin-resistant haemophilus. Mecillinam is active against Friedlander and

Aerobacter as are (sometimes) some of the cephalosporins including the newcomers cephacetrile, cephazolin, cefamandole and cephoxitin as well as cephalothin, cephaloridine and cephalexin. Cephaloglycine has, rightly, slipped into obscurity and one wonders if the same fate might or even should befall some of the newer derivatives.

2) Action on penicillinase-forming bacteria

Here there is less to report about the drugs though knowledge of the inactivating enzymes and their production grows impressively. Our Conference has given detailed attention to this problem, as the contributions of experts like Chabbert, Costerton, Richmond, Sabath, Voropaeva, Bobrowski and a number of others have shown in several of our sessions. Pride of place among the several useful penicillinase-stable anti-staphylococcal beta-lactams seems to belong still to cloxacillin though I am interested to note among the revivals that interesting derivative quinacillin, remarkable for its narrow selective action against staphylococci and resistance to hydrolysis by several forms of constitutive and inducible beta-lactamase.

3) Pharmacological improvements come from intensive attempts to produce and maintain better levels in blood, tissue-fluids and tissues by improved absorption or slower excretion. There is, commendably, more emphasis on oral medication. There is also, lamentably, a dearth of good information about the indications for parenteral therapy and about the conditions, technical and otherwise, under which the effects of such therapy are most beneficial. In this connection one welcomes the scrupulous pharmacological measurements of absorption, retention and excretion made by Meyer-Brunot and his colleagues in Germany. It is reassuring to note that some advantages can still be obtained by simple kitchen methods used by O.P.W. Robinson's expert chemical colleagues to produce talampicillin, the phthalyl ester of ampicillin. Quinn suggests an explanation for the high activity of cefazolin which attains levels in tissue and also in bile in excess of most other cephalosporins.

4) Reduced toxicity

The aim here must surely be to emulate or at least not to depart from the non-toxicity of penicillin G and ampicillin. This remarkable property is retained only when the side chain is kept simple as in these two substances. Differences and improvements nowadays come mainly from alterations or elaboration of the side chain. It is a fact of beta-lactam biochemistry that elaboration usually increases toxicity. So, without disrespect to most of the derivatives now available, one can say that almost any future alteration of the beta-lactam molecule is liable to

be an exercise in toxigenesis. To date, there is no evidence that any of the derivatives are less toxic than the simpler penicillins and cephalosporins. It is important therefore to remember - and occasionally in bad microbial situations to employ - the fact that penicillin G can be given in high dosage and maintained in the blood and tissues at very high levels for weeks on end without toxicity. One does read of occasional nephropathies and cephalopathies but these are still and always were exceptional. When organic toxicity does arise with benyl penicillin or with cephalothin it is most likely to be due to the cation (Na^+ or K^+) which can produce electrolyte imbalance in high doses. Some of the encephalopathies and neuropathies which I have seen or read about were almost certainly due to the procaine in procaine penicillin.

5) Allergy

This is now a rare disorder in the Western World. Among the reasons for reduction may be mentioned the removal of polymers, protein residues and other macromolecular complexes formed during manufacture or in storage. Such complexes can induce or elicit allergy in trace amounts. It was not realised therefore for many years that they were undetectable by the conventional methods of chemical and microbiological assay required by the B.P., U.S.P., F.D.A. and other regulatory agencies. Methods of assay and manufacture have now improved, but it is still possible in some countries or under some conditions for allergenic residues to be present in therapeutic preparations particularly since most beta-lactams, natural and semi-synthetic, tend to polymerise in solution to give macromolecules which serve as carriers for antigenic haptens formed from degradation products like penicillenates. We know a lot about the behaviour of penicillin G in this respect but very little about the new beta-lactams which tend to form antigenic fractions of baffling complexity. Syndromes such as the eosinophilic oliguria of methicillin and the mononucleosis rash of ampicillin have never been satisfactorily explained. There is a need to include in monitoring schedules some provision for immediate investigation of any untoward reactions even if they are seemingly transient. All beta-lactams are potentially immunogenic because they or their degradation products or polymers can act as haptens. Fortunately, the laws of hapten inhibition usually operate favourably, so the monovalent fractions and possibly the monomolecular drugs themselves act as inhibitors. When natural inhibitory mechanisms fail, the formol-lysine inhibitors described by de Week and his colleagues would appear to offer a promising and highly rational approach to prevention and control. Since cross-reactions between penicillins and cephalosporins appear to depend upon similarities in side chains rather than upon the common lactam structure, it will be logical to explore further the derivatives with non-benzyl and non thio-enyl side chains among the cepahlosporins.

Allergy is, as I have said, a rare difficulty nowadays. Its importance is that it is so often unpredictable and that it may still be severe or fatal. To guarantee safety, if beta-lactams must be used in hypersensitive subjects, it is wise to keep epinephrine and oxygen at hand and no advance has yet eliminated this necessity.

GENERAL ADVANCES

Most of the practical advances during the past 15 years have come from experimentation with derivatives of the 6-APA and 7-ACA molecular nuclei. There are, however, some backroom results which might well have a greater bearing upon future developments.

(a) Chemical improvements have led not only to the production of 6-APA by chemical methods from natural penicillin but also to the conversion of penicillins into cephalosporins.

(b) In the total synthesis of cephalosporins referred to by Abraham, the sulphur atom in the dihydrothiazine ring can be replaced by an oxygen atom to yield, for instance, an oxycephalosporin with activity comparable to cephalothin. This finding raises many interesting possibilities. We know, for instance, that the thio-enyl ring in cephalothin is equivalent in antimicrobial activity to an unsubstituted benzyl ring but it was not known that activity could be retained with loss of the reactive sulphur atom in the fused lactam ring. This could point to methods of stabilising the lactam structure as well as to losing the sulphur-linked degradation products which play a role in allergy and cross-reactions.

(c) The production from Streptomyces spp. of 7-methoxy analogues of cephalosporin C with a straight (d-alpha-amino-adipyl-) side chain points the way to interesting new structures, especially if benzyl or thio-enyl derivatives are used as side chains. Cefoxitin is one such which seems, according to Daikos and his colleagues in Greece, to have promising activity though it is not clear how well it compares in vitro and in vivo with its non-methoxy analogue.

It is impossible in a summary such as this to do justice to the many studies and advances which are being reported in world literature or even in that part which has been reported at this Conference. Ultimately, the struggle between host and germ depends upon natural processes of adaptation and resistance. In using antimicrobials medically, we intervene in a situation of growing epidemiological complexity. Often the most we know - if we even know that - is the immediate outcome. So for the sake

of safety as well as decency toward the future, we need to look where we are going. In this respect, our Conference has been better than most in its attempts during several sessions to assess the implications as well as the immediate results of the use of antimicrobials. When this is done with regard to penicillins and cephalosporins, as by Crain, Kunin, Gale, Howard and others, it is evident in terms of existing knowledge that this family of beta-lactam antibiotics is still by far the most important in background, present use and potential.