The Use of Antibiotics

A. Kucers

A Comprehensive Review
with Clinical Emphasis

Preface

This book aims to provide a concise, systematized description of antibiotics in current use in antibacterial chemotherapy. Commonly used synthetic antibacterial chemotherapeutic agents are included, but compounds used solely for tuberculosis and leprosy have been omitted. Although primarily designed for clinicians, the book may well be useful for bacteriologists, pharmacists, pharmacologists and undergraduates.

The presentation of a personal viewpoint has been consciously avoided, if this is possible, in favour of a balanced account of data and informed opinion from the medical literature. I have accordingly attempted to acknowledge all of my sources of information in the text.

Where conclusions are in doubt or controversial, the known facts and opinions are recorded for the reader to assess and apply in relevant circumstances.

Each chapter is devoted to one or several related drugs and divided into ten standard sections for ease of reference. A brief introductory description is followed by sections relating to the antibacterial spectrum, *in vitro* sensitivities, administration and dosage, serum levels, excretion, body distribution, mode of action, toxicity and clinical application.

Many colleagues, in particular the senior medical staff of Fairfield Hospital, have assisted with the preparation of this book. Dr. John A. Forbes, the Medical Superintendent and Dean of the Hospital Clinical School, encouraged me some six years ago to write, for use in our hospital, systematized notes on antibiotics which form the basis of this book. He has also read all of the manuscript, and has made many valuable suggestions. I would especially like to thank my colleague, Dr. Noel McK. Bennett, Specialist Physician and Deputy Medical Superintendent, who has been of immense assistance to me. He aided in the detailed editing of the text, and has contributed to much of the content of the book. Dr. Joan D. Schiavone, formerly Assistant Pathologist at Fairfield Hospital, now Senior Lecturer in the Department of Microbiology, University of Melbourne, has helped with many bacteriological aspects.

I would also like to thank my secretary, Mrs. Ann Cullen, for typing the manuscript and Miss Jean Foreman, the hospital medical librarian, for collecting much of the medical literature. I am also indebted to my

publishers, particularly Mr. Owen R. Evans, Managing Director, for advice on matters pertinent to medical publication, and for undertaking on my behalf the task of obtaining permission from other authors and publishers to reproduce tables and figures in the text.

A. Kucers

Melbourne, Australia
April 1972

Acknowledgements

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THE USE OF ANTIBIOTICS

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A. KUCERS, MB BS FRACP

Physician Fairfield Hospital, the Queen's Memorial Infectious Diseases Hospital, Melbourne, Australia, and the Clinical School for Infectious Diseases in Melbourne and Monash Universities

WILLIAM HEINEMANN MEDICAL BOOKS LTD
LONDON

First published 1972

ISBN 0 433 18875 8

Text set in 10/11pt. Monotype Times New Roman, printed by letterpress, and bound in Great Britain at The Pitman Press, Bath

Penicillin G

Description

Penicillin was isolated from Penicillium notatum by Fleming in 1929 and introduced into clinical medicine in 1941 by Florey, Chain and associates (Fleming, 1929; Chain *et al.*, 1940). The history of penicillin, including its early use in treatment of human infections, is described in an informative monograph on the penicillin group of drugs by Stewart (1965). Another very interesting account of the historical aspects has been written by Hare (1970).

The penicillin used by early workers was an amorphous compound containing impurities, which were introduced during the fermentative processes used in its manufacture, and its activity and dosage were expressed in units. The early penicillin was also a mixture of several penicillin compounds, designated as F, G, X and K. Penicillin G (benzylpenicillin) was found to be the most satisfactory, and this is now used in a highly purified and crystalline form for clinical purposes. Penicillin G as such is a rather unstable acid, and the following relatively stable salts are currently used clinically:

1. *Sodium penicillin G or sodium benzylpenicillin.* This is a highly soluble salt, and a dose can be dissolved completely in a few mls of water prior to administration. The dosage of this and other penicillin G preparations is still commonly expressed in units. One unit of activity is equal to 0·6 mcg of pure sodium penicillin G.

2. *Potassium penicillin G* similarly is a very soluble salt, but it is now rarely used. One unit of activity is equal to 0·625 mcg of pure potassium penicillin G.

The term "crystalline penicillin G" or simply "crystalline penicillin" is nowadays often used as a synonym for either of the above highly soluble benzylpenicillin salts, but all other penicillins in use are also crystalline in form, unlike the early impure amorphous compound.

3. *Procaine penicillin G* (*Procaine benzyl-penicillin or procaine penicillin*). This is a much less soluble salt, and it is administered intramuscularly as a suspension of crystal particles. These particles dissolve slowly after administration, so that absorption from the injection site takes place over a prolonged period. One unit of activity is equal to 1·0 mcg of pure procaine penicillin.

4. *Benzathine penicillin G* (*Di-benzyl-ethylene-diamine penicillin or DBED penicillin*). This salt is even less soluble than procaine penicillin, so it is even more slowly absorbed from an intramuscular injection site. One unit of activity is equivalent to 0·75 mcg of the pure substance.

The procaine and benzathine salts of penicillin G are known as the "long acting", "depot" or "repository" forms of penicillin G.

Sensitive Organisms

1. *Gram-positive cocci.* Penicillin G is highly active against many of these bacteria. Strep. pyogenes is always very sensitive, and sensitivity testing is not required. The same has been held to be true for Dip. pneumoniae, but recently relatively resistant pneumococcal strains (requiring about a twenty-five times higher penicillin G concentration for inhibition than sensitive strains) have been isolated from patients in New Guinea and Australia (Hansman *et al.*, 1971). These isolated findings at present do not appear to justify routine penicillin sensitivity testing of pneumococci (Finland, 1971) but it would seem advisable for reference laboratories in various parts of the world to monitor the local sensitivity pattern of this organism.

Anaerobic streptococci are nearly always highly sensitive to penicillin G. Most Strep. viridans strains are also very sensitive, but resistant variants have been found, particularly in the pharynx of patients taking prophylactic penicillin for prolonged periods (Sprunt *et al.*, 1968). Strep. faecalis, compared to the other streptococci, is less sensitive to penicillin G (Table 1) and sometimes may be highly resistant, and therefore sensitivity testing is required.

Many strains of Staph. pyogenes, even outside hospitals, are resistant to penicillin (Bennett and Kucers, 1970). Staphylococcal resistance to penicillin is usually due to penicillinase production and other mechanisms are rare. The commonly employed disc sensitivity testing method classifies staphylococci into either penicillin-sensitive (penicillinase-negative) or penicillin-resistant (penicillinase-positive) categories, but it has been shown that this resistance is not necessarily an all or none phenomenon. It appears that sometimes a staphylococcal population may be mixed and contain a variable proportion of organisms which are resistant to penicillin in varying degrees. If staphylococcal sensitivity testing is performed by a special agar dilution method, some strains are found to be highly sensitive, others resistant, but many fall in an intermediate range (Alexander, 1968). Penicillin G may well be a useful therapeutic agent for infections due to the latter group (normally classified as penicillinase-producing and penicillin G-resistant by the disc test), provided that large doses of penicillin G are used in combination with another antistaphylococcal agent (Sprunt, 1971). Similarly

other workers have found that penicillin G and sodium fusidate act "synergistically" against penicillin-resistant staphylococci, if the Staph. pyogenes strain is not a highly active penicillinase-producer (page 191). However, most clinicians nowadays use penicillin G only for treatment of infections due to penicillinase-negative staphylococcal strains, and select a penicillinase-resistant penicillin or another chemotherapeutic agent for the others.

2. *Gram-positive bacilli.* Cl. tetani, Cl. perfringens (welchii), C. diphtheriae, B. anthracis, and Listeria monocytogenes are consistently sensitive to penicillin G.

3. *Gram-negative cocci.* Neisseria meningitidis and N. gonorrhoeae are both sensitive to penicillin G. Penicillin resistance of N. meningitidis has so far not been reported, but relatively resistant gonococcal strains are encountered with increasing frequency (Leading article, 1969; Martin *et al.*, 1970). The less common human pathogen, Mima polymorpha may be penicillin-sensitive (Goldstein *et al.*, 1965), but is more commonly resistant (Olafsson *et al.*, 1958).

4. *Gram-negative bacilli.* The Enterobacteriaceae, such as Esch. coli, and Salmonella, Shigella, Enterobacter, Klebsiella and Proteus spp. and those of the Paracolon group, are resistant to penicillin G. The same applies to other Gram-negative bacilli such as Brucella and Pasteurella spp., Vibrio cholerae, Pseudomonas aeruginosa, Bacteroides spp. and others. H. influenzae and B. pertussis are also usually described as penicillin G-resistant, but these bacteria are inhibited by relatively low penicillin concentrations (Table 1). The resistance of the Gram-negative bacilli to penicillin is one of degree. Thus, Weinstein *et al.* (1964) classify these organisms as "sensitive" is they are susceptible *in vitro* to 2·5–78 units of penicillin G per ml, as "moderately sensitive", if they are inhibited by 156–625 units per ml, and as "resistant" if they are inhibited only by 1250 units per ml or more. On the basis of this classification, about 83 per cent of Esch. coli strains tested by these authors were "sensitive", Proteus mirabilis always "sensitive", but Pr. vulgaris was usually "resistant", and Ps. aeruginosa always "resistant". The salmonellae and shigellae tested fell in the "sensitive" group.

The resistance of certain of the Gram-negative organisms, e.g. Esch. coli, is associated with their ability to produce enzymes (beta-lactamases) which destroy penicillin G (Pollock, 1965).

5. Treponema pallidum and the Leptospirae are consistently sensitive to penicillin G.

6. Streptobacillus moniliformis and Spirillum minus (the organisms causing rat-bite fever) are nearly always sensitive to penicillin G. Actinomyces are also sensitive, but the Nocardia are not. All the true fungi are resistant.

7. Mycobacteria, Mycoplasmas, Rickettsiae and Protozoa such as Entamoeba histolytica are all completely penicillin-resistant.

In Vitro Sensitivities

The minimum inhibitory concentrations of penicillin G against some selected bacterial species are shown in Table 1. They are given in micrograms per ml, but penicillin G is still usually prescribed in units.

TABLE 1

Compiled from data published by Welch (1954), Garrod (1960a and b), Knox (1960), Barber and Waterworth (1962), and Sutherland *et al.* (1970)

Organism	Usual Minimum Inhib. Conc. in mcg per ml
Gram-positive bacteria	
Staph. pyogenes (non-penicillinase producer)	0·03
Strep. pyogenes (Group A)	0·007
Strep. pneumoniae (Dip. pneumoniae)	0·015
Strep. viridans spp.	0·01
Strep. faecalis (Enterococcus, Group D)	2·0
Bacillus anthracis	0·015
Clostridium tetani	0·06
Corynebacterium diphtheriae	0·062
Gram-negative bacteria	
Salmonella typhi	4·0
Shigella spp.	16·0
Escherichia coli	64·0
Proteus mirabilis	32·0
Neisseria gonorrhoeae	0·007
Neisseria meningitidis	0·03
Haemophilus influenzae	1·0
Bordetella pertussis	0·5
Brucella abortus	6·0
Miscellaneous	
Treponema pallidum	0·03
Leptospira icterohaemorrhagiae	0·6
Actinomyces israeli	0·05

As one unit is equivalent to 0·6 mcg of pure sodium penicillin G, the MIC's expressed in units per ml are about 1·7 times higher than shown in the table.

Mode of Administration and Dosage

1. Penicillin G is destroyed by acid in the stomach and therefore absorption after oral administration is irregular and variable.

Intramuscular injection is the usual method of administration, but the highly soluble salts of penicillin G can also be given intravenously.

2. *Crystalline penicillin G.* For initial treatment of severe or moderately severe infections crystalline penicillin G may be administered every six hours or even more frequently. A common adult dosage is 1,000,000 units (0·6 gm) crystalline penicillin G intramuscularly or intravenously six hourly. For serious infections much higher doses can be given, e.g. for meningitis a common starting dose in adults is 3,000,000 units (1·8 gm) three hourly. Doses higher than this are usually unnecessary for infections, however severe, caused by penicillin-sensitive organisms. "Massive" penicillin doses of up to 100 million units (60 gm) daily intravenously, however, are occasionally used for serious infections due to relatively resistant organisms, e.g. Strep. faecalis endocarditis (though a lower dose usually suffices when a penicillin G/streptomycin combination is used), or infections due to Gram-negative bacilli (Weinstein *et al.*, 1964). Conversely some authors consider that a dose such as 1,000,000 units IM six hourly is unnecessarily high for many infections of moderate severity. Thus Anderson *et al.* (1968) consider an adult dose of crystalline penicillin as low as 300,000 units IM twelve hourly satisfactory for treatment of pneumococcal pneumonia, a disease in which the blood supply to all diseased areas is very good. Such small penicillin doses entail risks and are not generally advocated. It is interesting that doses now regarded as inadequate (e.g. 15,000 units four hourly) were lifesaving in very severe infections during the early years of penicillin (Stewart, 1965), but the results of treatment appear to have improved since that time.

3. *Method of intravenous administration.* The administration of sodium penicillin G intravenously may be carried out by continuous infusion or intermittent injections of the drug into the intravenous tubing. In emergency treatment of serious infections an initial direct injection of penicillin G should be given intravenously to achieve a high level of penicillin quickly, and this could then be followed by continuous penicillin infusion. Some considered continuous infusion preferable because of rapid renal excretion of the drug and the increased hazard of thrombophlebitis with intermittent administration (Welch, 1954). However, various problems may arise if penicillin is added to intravenous fluid bottles. Penicillin may be incompatible with other additives to the intravenous solutions. For instance Simberkoff *et al.* (1970) have shown that penicillin G and semisynthetic penicillins are almost completely inactivated within a few hours in carbohydrate solutions containing sufficient bicarbonate to elevate the pH above 8·0. Furthermore, penicilloic acid, which appears to have a role in some of the allergic reactions, is a major product of such inactivation. Most clinicians therefore now prefer intermittent intravenous injections or at

least intermittent rapid infusions of high concentration penicillin solutions. (See comments re intravenous methicillin, page 39.)

4. *Procaine penicillin.* During the later stages of treatment of many infections (e.g. scarlet fever and pneumonia) procaine penicillin can be substituted for crystalline penicillin. Procaine penicillin is useful because the absorption of an injected dose continues for up to 24 hours, so injections may be separated by this interval, but lower serum levels are obtained. Injections of this preparation are also less painful than crystalline penicillin. A common adult dosage for procaine penicillin is 1,000,000 units IM once or twice a day. In milder infections procaine penicillin may be satisfactory for initial treatment. This compound must not be given intravenously.

5. *Children.* The doses of crystalline or procaine penicillin should be adjusted according to age and weight. For children under three years of age ¼ of the adult dose and for older children ½ the adult dose are suitable.

6. *Newborn and premature infants.* The renal clearance of penicillin G in this age group is reduced to about 20 per cent of the clearance values in older children and adults. Therefore small doses of crystalline penicillin given at twelve hourly intervals are recommended (e.g. 50,000 to 100,000 units IM twelve hourly). The use of procaine penicillin in newborns is inadvisable because it tends to produce sterile injection abscesses (Yaffe, 1965).

7. *Patients with renal failure.* Penicillin G is often administered in the usual doses to these patients because there is no great risk of toxicity from accumulation. However, moderately large intravenous doses may yield toxic levels necessitating dosage reduction (Plaut *et al.*, 1969).

8. *Benzathine penicillin,* when injected intramuscularly in doses of 600,000 to 1,200,000 units, maintains a low serum concentration of penicillin for a period of one to several weeks. Single injections of this preparation in these doses have been used for treatment of gonorrhoea and syphilis, and monthly injections are sometimes used for rheumatic fever prophylaxis.

8. *Oral administration of potassium penicillin G* or *benzathine penicillin G* has been used in children, but the acid stable phenoxypenicillins (page 27) are now preferred for oral therapy. The loose term "oral penicillin" now usually applies to penicillin V or one of its homologues.

Preparations Available

1. *Crystalline penicillin G,* suitable for IM or IV administration, is available as either the sodium or potassium salt of penicillin G. For parenteral therapy the sodium salt is now usually used, and vials of 0·5, 1·0, 1·5, 2·0, 5·0 and 10·0 mega units (0·3, 0·6, 0·9, 1·2, 3·0 and 6·0 gm) are available. Potassium penicillin G is also available for oral administration, e.g. in 250 mg capsules, but this is now rarely used.

2. *Procaine penicillin* for IM use only.
   (*a*) Aqueous suspension of procaine penicillin, containing 300,000 units per ml. This is now most commonly marketed in disposable syringes, each containing either 0·6, 1·0 or 1·5 mega units or gms of procaine penicillin.
   (b) Fortified aqueous suspension, which contains added crystalline penicillin G.
   (c) Oily suspension containing procaine penicillin and aluminium monostearate. The absorption of this product is even more delayed but tissue damage may be a problem. This is now rarely used.

3. *Benzathine penicillin.* Pure benzathine penicillin is available in suspension containing 600,000 units per ml for IM administration. In addition vials of a mixture containing benzathine penicillin 450 mg (600,000 units), procaine penicillin 300 mg (300,000 units) and potassium penicillin 187 mg (300,000 units) ("Bicillin all purpose", Wyeth) are available for IM use. Tablets of benzathine penicillin (e.g. "Bicillin" Wyeth, 150 mg) are available for oral administration, but like oral potassium penicillin G, these are now rarely used, the phenoxypenicillins (page 27) being preferred for oral penicillin therapy.

4. *Purified benzyl-penicillin (BRL 3000 or "Purapen G").* Vials of 0·5 and 1·0 mega units are available for intramuscular or intravenous administration. This preparation has been developed by Beecham Research Laboratories. Work at these laboratories (Batchelor *et al.*, 1967; Knudsen *et al.*, 1967) confirmed by Stewart (1967) has shown that standard preparations of the penicillin nucleus, 6-amino-penicillanic acid and penicillin G still contain high molecular weight impurities. These are inactive against bacteria, but evoke reactions in hypersensitive patients. Knudsen *et al.*, (1967) carried out cutaneous sensitivity tests in ninety-five volunteers with a previous history of penicillin hypersensitivity using both ordinary penicillin G and "purified penicillin", from which these impurities had been removed. Eleven subjects reacted only to ordinary penicillin, nine reacted to both, whilst one had a positive reaction to the purified benzylpenicillin only. This purified product is now available as "Purapen G". It is unlikely that it is entirely safe for use in penicillin allergic patients; indeed, a proportion will possess antibodies directed to some other component (page 12). The role of "Purapen G" in clinical medicine at present lacks definition. Chain (1970) expressed the opinion that the use of this purified penicillin would probably reduce the incidence of sensitization in patients not yet allergic to penicillin. However, currently "Purapen G" is more than twice as expensive as ordinary crystalline penicillin and it has not been widely used. It would be reasonable to use purified benzylpenicillin in patients with a history of penicillin sensitivity who are suffering from severe infections where penicillin is the drug of first choice. Cooper *et al.* (1968) have reported the successful use of large doses of "Purapen G" intravenously in a patient with known penicillin hypersensitivity.

Serum Levels in Relation to Dosage

1. *Intravenous crystalline penicillin G.* Immediate high blood levels are attained after rapid intravenous injection of this preparation. Plaut *et al.* (1969) studied penicillin serum levels serially in ten patients with normal renal function, who received an intravenous injection of 3 gm of sodium penicillin G (5 million units) during a 3 to 5 min period. The resulting mean serum concentration after 5 min was 400 mcg per ml and after 10 min 273 mcg per ml. During the first hour there was a rapid decrease in the serum concentrations (due to both distribution and elimination of the drug), and at the end of the hour the mean serum level was 45 mcg per ml. The subsequent fall in serum levels was