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Drug Safety in Clinical Practice

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With 24 Figures

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Peter I. Folb, MD, FRCP

Professor of Pharmacology,
University of Cape Town Medical School;
Chief Physician, Groote Schuur Hospital,
Cape Town.

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Preface

Drugs may cause disease, or they may aggravate the morbidity of the condition for which they are prescribed, and certain patients may for one or other reason be particularly liable to drug injury. The inextricable relationships between the toxic profiles of drugs, the natural history of the diseases for which they are given, and the adverse drug effects that may develop in the course of such diseases are of considerable interest. It is the study of these rather neglected aspects of pharmacology and therapeutics which has formed the basis of this book.

An explanation is required of the approach and the style which have been followed. The monograph does not purport to be comprehensive. Only important drug groups which are commonly used in practice are considered. Emphasis has been placed on achieving maximum benefit and safety of the appropriate drugs in the management of common illnesses. When treatment fails, either *ab initio* or subsequent to an initial response, the risk-benefit relationship of drugs inevitably alters. For this reason the main factors responsible for treatment failure have been considered, with special attention to the possible contribution of or implications for drug therapy in such a situation. Finally, proposals have been put forward for improving the diagnosis and reporting of adverse drug effects.

In order to be practical and, as far as possible, constructive it has been necessary for me to "take a position" on numerous issues. In many instances I have expressed a point of view based on my understanding of authoritative literature (cited at the end of each section) and such clinical experience as I may have gained or have accrued from colleagues. There is a danger that this approach will be seen as somewhat categorical. I hope, however, that it may be understood as an attempt to depart from the descriptive and encyclopaedic approach which has tended to characterise medical writing in this particular field.

My colleagues John Straughan and Ashley Robins have in particular given me helpful advice, and I am grateful to Michael Jackson of Springer-Verlag who has guided the original idea behind

the book to fruition. Renée Gelbart and June Chambers have given me much assistance in the compilation of material. Elise Fuller helped with the illustrations. The Medicines Safety Centre of the University of Cape Town Medical School, jointly sponsored by Ciba Geigy, has been a source of valuable information.

The South African Medical Research Council and the University of Cape Town have supported my researches into mechanisms and models of drug-induced damage, and this help is gratefully acknowledged.

Cape Town, 1983 Peter I. Folb

Contents

1 Drugs in Common Use

1.1 Antibiotics

The following *ground rules* for the use of antibiotics would contribute to optimising their benefit-risk relationships:

1. When adverse effects may have been experienced with previous antibiotic therapy, an alternative equally effective antibiotic of a different generic group is sought.
2. In selecting an antibiotic its clinical pharmacokinetics are considered, with special attention paid to transfer across the blood-brain barrier and distribution and elimination in renal failure and hepatic disease.
3. Combination therapy is administered only when a synergistic effect can be achieved. Unnecessary combination of antibiotics heightens the risks of toxicity, favours selection of resistant organisms, and represents additional expense, without contributing to a simpler regimen.
4. Bactericidal and bacteriostatic antibiotics are not combined (Table 1.1). This may result in a bacteriostatic effect alone, as the bactericidal activity of certain antibiotics is dependent upon rapid division of bacterial cells.
5. Antibiotics with similar toxicity profiles, which are known to cause adverse effects on the same organ, are not given together.
6. Antibiotic therapy for fever of undetermined origin is avoided as far as possible. Fever of several days' duration which is not associated with clinical signs of infection is usually due to viral infection, often of the respiratory tract, which will not respond to antibiotics. Prolonged fever, when it has an infectious cause, is most commonly due to tuberculosis or bacterial endocarditis. In either case blind use of antibiotics is likely to delay diagnosis and increase the risk of extensive damage.
7. The use of topical antibiotics (with the exception of use in the eye) is probably an important contributory factor to the development of antibiotic resistance of micro-organisms. Suitable alternatives may be effectively used for mild superficial infections. Severe skin infections are properly managed by systemic antibiotic therapy.

Table 1.1. Classification of antibiotics according to bactericidal or bacteriostatic activity (based on Reiner 1982)

Group I: Bactericidal, partially also on resting micro-organisms	Group II: Bactericidal, only on proliferating micro-organisms	Group III: Bacteriostatic, in high concentrations also bactericidal
Polymyxins	Penicillin	Chloramphenicol
Streptomycin	Cephalosporins	Thiamphenicol
Neomycin	Vancomycin	Tetracyclines
Kanamycin	Rifampicin	Fusidic acid
Gentamicin		Erythromycin
Sisomicin		Lincomycin
Netilmicin		Clindamycin
Tobramycin		
Amikacin		

Notes:

1. The activity of an antibiotic combination can differ, depending on the components concerned, viz:
   - *Indifference* — the activity of the combination is equal to that of the more active component.
   - *Addition* — the activity of the combination is equal to the sum of the activities of the components.
   - *Synergism* — the activity of the combination is significantly greater than the sum of the components.
   - *Antagonism* — the activity of the combination is less than that of the more active component.
2. The combination of antibiotics *within* groups I and II usually does not display antagonism.
3. The combination of an antibiotic of group I with one of groups II or III rarely gives rise to antagonism. In general, the bactericidal agent predominates.
4. The combination of an antibiotic of group II with one of group III frequently leads to dominance of the bacteriostatic agent, i.e. the activity of the combination corresponds to the activity of the agent of group III. Antagonism is possible.

8. Prophylactic antibiotics, frequently given despite inadequate evidence that they are effective, may generate problems of toxicity and microbial resistance.

   The case for prophylaxis in rheumatic fever and bacterial endocarditis is established, and a good argument can be made for prophylaxis in meningococcal infections, diphtheria, to cover urological procedures, recurrent urinary tract infections, severe cases of chronic bronchitis, and patients with "healed" or "inactive" tuberculosis at special risk. Prophylactic antibiotics are widely used in hip replacement and vascular surgery.

9. It is important that an antibiotic is selected which has the narrowest effective range for the micro-organism or micro-organisms responsible for the infection being treated. The antibacterial range of antibiotics in common use is indicated in Fig. 1.1. For severe infections, antibiotics are ideally administered parenterally in the first instance.

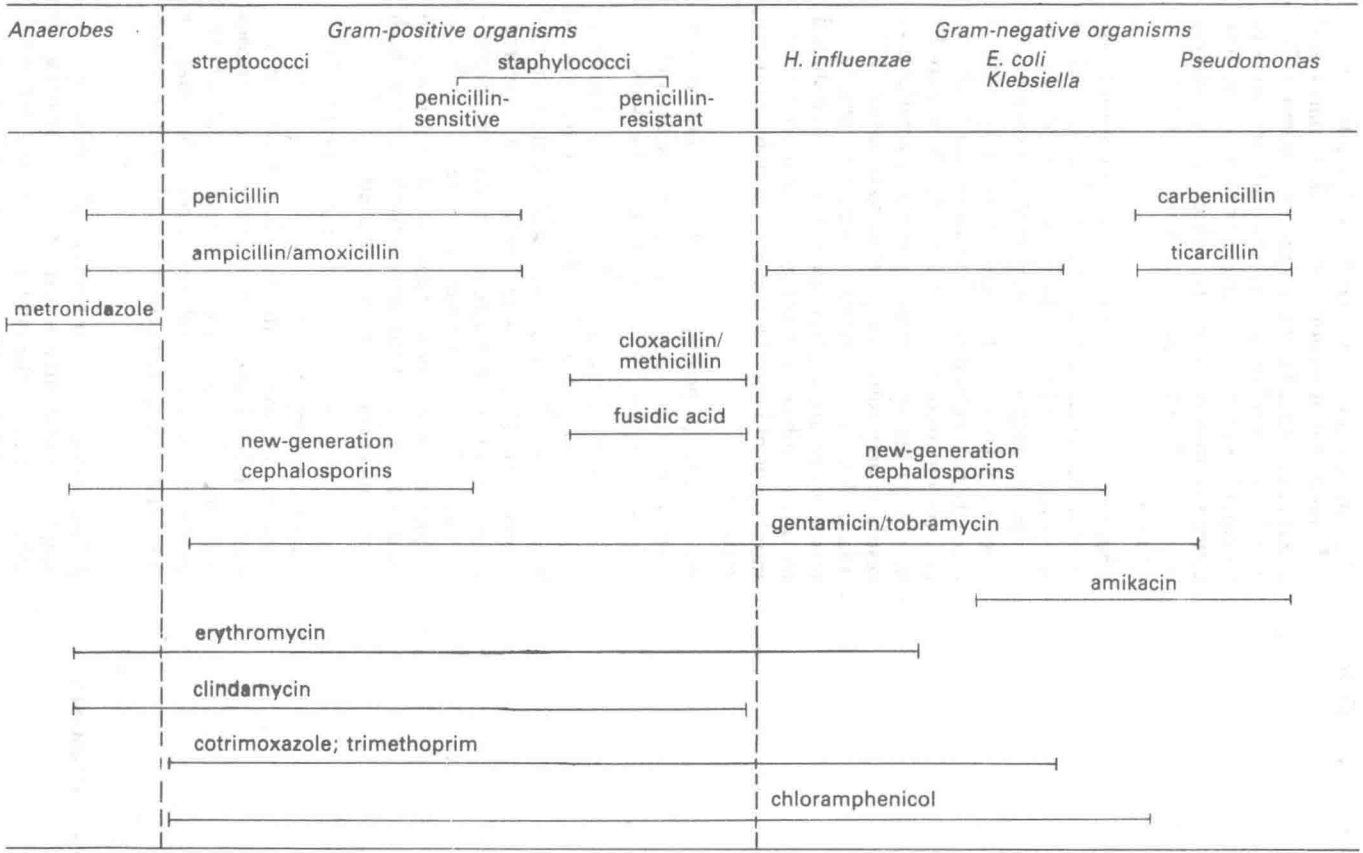

Fig. 1.1. Suggested use of common antibiotics.

Topical Antibiotics

The efficacy and safety of topical application of antibiotics for infections of the skin, nares and external ear have been brought into question. For mild local infections antiseptic agents are likely to be equally effective. In severe infections the low concentrations of antibiotic achieved are unlikely to be sufficient, and systemic treatment is necessary.

There is convincing evidence that the topical use of aminoglycosides and other antibiotics such as tetracyclines and fusidic acid contributes to bacterial resistance. Suboptimal concentrations lead to selection of bacterial variants with a capacity to inactivate the drug or reduce antibiotic penetration into the bacterial cell. There may be an abrupt one-step development of resistance as a result of acquisition of extra-chromosomal DNA (plasmids). The acquired microbial resistance towards one aminoglycoside is likely to be shared by other antibiotics of the group, and not uncommonly plasmid transfer confers multiple antibiotic resistance.

As a general principle, no antibiotic which is used systemically (or is closely related to one used systemically) is applied to the surface of the body.

The eye is an exception to these general considerations. The sequelae of ocular infections may be serious, and the organisms most feared in this respect are *Pseudomonas aeruginosa*, *Streptococcus pneumoniae* and penicillin-resistant staphylococci. The penetration of agents such as sulphacetamide, chloramphenicol and gentamicin (the latter injected subconjunctivally) enable high local concentrations to be achieved.

Certain antibiotics such as the peptides (bacitracin, polymyxins and tyrocidine), polyenes (nystatin and pimaricin) and clotrimazole are not significantly absorbed from the skin or mucous membranes. They are practically free of the problems of microbial resistance; this may be attributable in part to their limited use in practice.

Beta-Lactamases:

β-Lactamase was originally identified as the staphylococcal enzyme capable of destroying the β-lactam ring of the penicillin nucleus, thus rendering the antibiotic inactive. With the development

and widespread use of broad-spectrum, semi-synthetic penicillins and cephalosporins, penicillin- and cephalosporin-resistant Gram-negative bacteria emerged which produced a β-lactamase different to that of staphylococci. The latter is cell-bound, and confers a permeability barrier which protects the bacterial cell from antibiotic destruction. (The production of a β-lactamase in small amounts is a characteristic of many Gram-negative bacteria; it may be necessary for normal growth of the organism.)

Amongst the Gram-negative bacteria the β-lactamases can be broadly classified into:

i) Those that preferentially hydrolyse penicillins with little anti-cephalosporin activity ("penicillinases").

ii) Those that hydrolyse cephalosporins with little anti-penicillin activity ("cephalosporinases").

iii) "Broad-spectrum" β-lactamases that hydrolyse both penicillins and cephalosporins to a considerable extent.

Most penicillinases destroy benzylpenicillin, penicillin V, ampicillin, amoxicillin and carbenicillin. No β-lactam antibiotic is completely resistant to the β-lactamases. The degree of penicillinase and cephalosporinase production of various micro-organisms is indicated in Table 1.2.

Table 1.2. β-Lactamase production by various micro-organisms

	Penicillinase	*Cephalosporinase*[a]
Staph. aureus	++++	+++ →+
Ps. aeruginosa	++++	++ →+
Proteus sp.	+++	+ →+
Haemophilus influenzae	++++	+++ →+
Klebsiella sp.	++++	++ →+
Bacteroides fragilis	++++	++++→+

[a]The cephalosporinases are less effective against the new-generation cephalosporins.

Side-effects

A distinction can be made between (a) dose-related adverse effects that are predictable from the pharmacological action and toxicity profile of an antibiotic or from biological effects due to growth inhibition of the normal bacterial flora, such as is

frequently encountered with broad-spectrum antibiotics, and (b) allergic reactions, which are dose-independent and in the main not predictable.

A profile of side-effects of different antibiotics and chemotherapeutic agents is given in Table 1.3.

Table 1.3. Side-effects of antibiotics and chemotherapeutic agents

Antibiotic or chemotherapeutic agent	Side-effects					Contra-indicated or to be used with considerable caution in advanced renal insufficiency
	Allergic	Haemato-toxic	Nephrotoxic	Hepatotoxic	Neurotoxic	
Penicillin	++(1)				+	
Flucloxacillin; dicloxacillin	++				±	
Amoxicillin; ampicillin	++				±	
New cephalosporins	+(1)	±				
Chloramphenicol	±	+(2)			±	
Aminoglycosides(3)	+		+(4)		++(5)	X
Tetracyclines	±	±		±		X(6)
Erythromycin; clindamycin(7)	±			±		
Fusidic acid	±					
Vancomycin	++		+		+	X
Sulphonamides; cotrimoxazole	++	±	±	±		

Key: ± = rare; + = uncommon; ++ = relatively frequent
Numbers refer to the following notes

Notes:

1. For discussion of allergic reactions to the penicillins and cephalosporins refer to p. 00.
2. Chloramphenicol depresses the bone marrow by one of two mechanisms:
   i) A dose-related reversible effect mainly on the formation of red cells, but at times also platelets and granulocytes; and
   ii) Severe aplasia with pancytopenia, which is uncommon, unpredictable, not dose-related, and idiosyncratic.

   The former appears to be due to inhibition of mitochondrial protein synthesis. The latter probably results from a genetically determined biochemical predisposition (a defect in nucleic acid synthesis has been suggested).
3. The comparative toxicity of the aminoglycosides is set out below:

Antibiotic	Effects on:			
	Vestibulum	Cochlea	Kidney	Neuromuscular blocking
Streptomycin	+++	+	+	++
Dihydrostreptomycin	+	+++	+	+
Neomycin	+	++++	+++	+++
Framycetin	+	++++	+++	+++
Kanamycin	+	+++	++	+++
Gentamicin	++	+	++	++
Tobramycin	++	+	++	++

4. The risk of aminoglycoside nephrotoxicity is greater in the following circumstances: concomitant treatment with other potentially nephrotoxic antibiotics (e.g. vancomycin); treatment in excess of 10–14 days; serious coexistent disease such as coagulopathy, bleeding, shock, dehydration and urate nephropathy (in cancer patients on cytotoxic treatment).
5. The aminoglycosides destroy the sensory hair cells in the inner ear (organ of Corti of the cochlea). The risk of aminoglycoside ototoxicity is greater with concomitant use of high-ceiling diuretics, usage in excess of 10 days, renal disease with decompensation, high dosage, recent aminoglycoside therapy, pre-existing ear disease and in patients older than 40 years.

   Delayed ototoxicity may occur even after treatment has been discontinued. This is thought to be due to the persistent toxic effect of accumulated drug in the inner ear and semicircular canals. Unilateral aminoglycoside ototoxicity has been described. Topically administered aminoglycosides in the ear may account for some deafness complicating otitis media.

   Even the "non-absorbable" aminoglycosides such as neomycin can be absorbed from the gastrointestinal tract or following intrabronchial or intraperitoneal administration in sufficient amounts to cause deafness. This is likely when there is coexistent renal insufficiency and the antibiotic cannot be normally eliminated.
6. Doxycycline can be administered in renal insufficiency, although appropriate dosage adjustments are necessary in advanced failure (see Table 1.4), and because of poor filtration into the urine it is unlikely to be effective in urinary tract infections in such patients. (Between 60% and 70% of the other tetracyclines is excreted in the urine; 35%–40% of a dose of doxycycline is excreted in the urine.)
7. A serious potential side-effect of clindamycin therapy is pseudomembranous colitis.

Renal Elimination

Many antimicrobial agents are eliminated primarily by the kidneys. The aminoglycosides, the polymyxins and vancomycin are exclusively eliminated by renal mechanisms and their toxicity correlates directly with concentrations in plasma and tissues. Since the adverse effects of these antibiotics involve the kidneys a vicious cycle may develop if they accumulate in the body.

Tetracyclines accumulate in patients with impaired renal function, with the exception of doxycycline. Uraemia may be aggravated by the catabolic effect of elevated amounts of tetracycline.

A guideline for dosage adjustments for patients in renal failure is given in Table 1.4.

Hepatic Disease and Failure

The dosage of antibiotics excreted by the liver (erythromycin, chloramphenicol, lincomycin, clindamycin and doxycycline) must be reduced in patients with hepatic failure.

If there is infection in the biliary tract, hepatic disease or biliary obstruction may reduce access of an antibiotic to the site of the infection. This has been shown to occur with several drugs normally excreted in the bile.