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EDITORIAL

The Future of β-Lactam Antibiotics

Historical landmarks of major technical discoveries are continuously reevaluated by newer research technologies, and this principle also holds true with antibiotics. Thus, recent fluorescence studies have identified the presence of tetracycline in Nubian bones recovered from a Sudanese cemetery [1]. This discovery predates the antibiotic era by more than 1,500 years and will be hard to top. As far as β-lactam compounds are concerned, their official history is just a little over 50 years old; they can be traced back to Fleming's genial interpretation of the interaction between the mold *Penicillium* and *Staphylococcus aureus* in 1928 [2]. Since then, microbiologists and organic chemists have purified and synthesized thousands of variants of the original molecule, and sizable numbers of them have found clinical application. Thus, the "β-lactam-tree" summarized in 1979 [3] has continued its dramatic growth, and two years later it already shows a large number of new twigs budding off, including the oxa-β-lactam compound moxalactam. But just as trees have to be regularly inspected and pruned, it is our task to cast sometimes a critical view on this β-lactam family to eliminate redundant or obsolete compounds and to foster the development of novel agents with hitherto unknown biological or biochemical properties.

Of the many present and future aspects of the β-lactam compounds, this discussion will concentrate merely on two groups of problems that will, in my opinion, receive growing attention in the future. First, it is more than likely that new β-lactam compounds that are active against resistant nosocomial gram-negative organisms will be developed that will exhibit antibacterial activity at concentrations as low as those encountered for the action of penicillin G against group A streptococci. Such a development will certainly decrease the need for and use of more toxic antibiotics in noncompromised hosts; whether their use as single drugs in compromised hosts will become common medical practice is, and probably will remain, an unsettled question. To replace some of the more toxic compounds, however, these new β-lactam antibiotics will have to keep the basic toxicologic and pharmacologic properties of the penicillin G molecule.

Second, further rapid progress can be foreseen in the evaluation of the properties and investigation of the modes of action of the β-lactam antibiotics. Determination of bacteriostatic and bactericidal end points (MICs and MBCs, respectively) against pathogens seems indeed to be a crude and controversial way of assessing new antibiotics. New approaches, such as identification of the species specificity of the various penicillin-binding proteins, of the enzyme systems susceptible to these antibiotics, and of possible inactivating enzyme systems, as well as demonstration of the early biochemical and morphologic changes occurring prior to cell death, will help to discover more active substances and lead to the identification of new and as yet unknown modulating effects of the β-lactam antibiotics on the pathogenicity of microorganisms.

Development of β-Lactam Antibiotics Active Against Gram-Negative Organisms

Since β-lactamase–negative gram-positive organisms are inhibited and killed by concentrations of penicillin G ranging from 0.01 to 0.05 μg/ml, it seems unrealistic to expect any future compound to have a higher efficacy against these organisms [4]. This expectation is only partly true for semisynthetic compounds such as the isoxazolylpenicillins, which exert their antibacterial effects on most β-lactamase–producing staphylococci at microgram concentrations [5] and are of unpredictable efficacy against the many emerging, resistant strains of *Staphylococcus epidermidis*. Moreover, the failure rate for severe staphylococcal infections is still considerable and might be partly related to the problem of tolerance of these organisms to a variety of bactericidal antibiotics. Thus, there is still room for improvement at this end of the antibacterial spectrum, and more bac-

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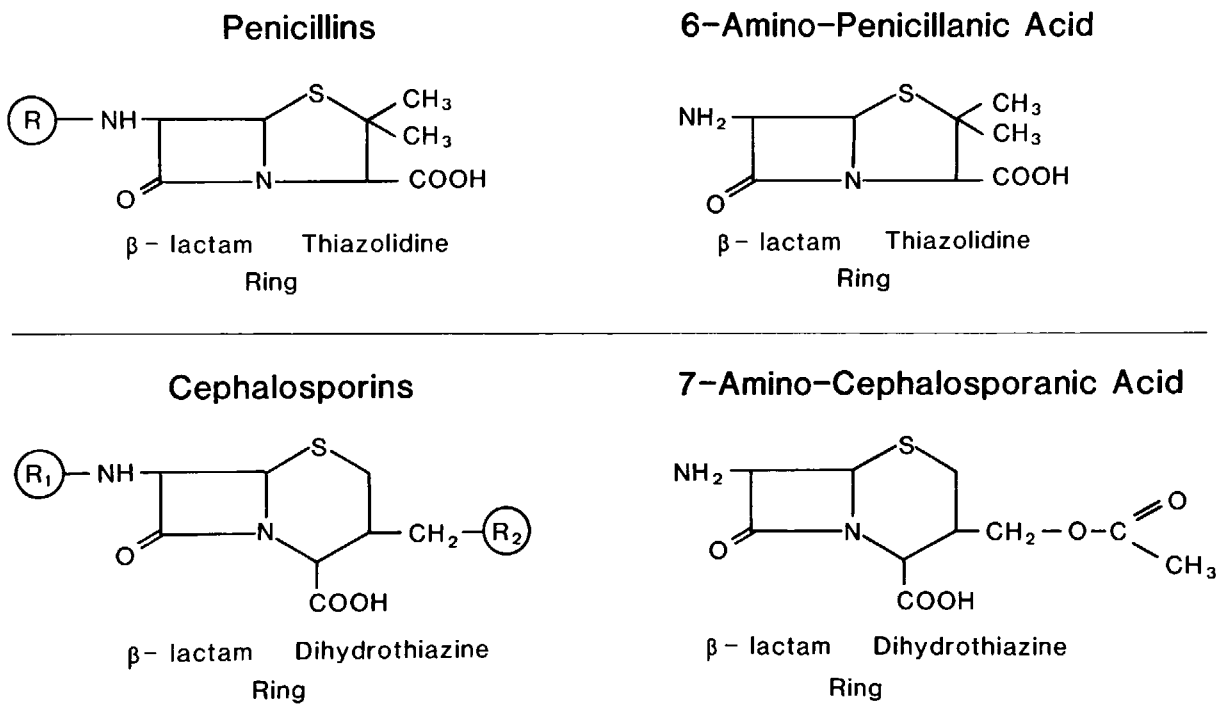

Figure 1. Structure of (*top*) penicillin and its basic fermentation product, 6-amino-penicillanic acid, and (*bottom*) cephalosporin C and its basic fermentation product, 7-amino-cephalosporanic acid. R, R1, and R2 indicate variable side chains.

tericidal antistaphylococcal β-lactam compounds with low toxicity are awaited with interest.

What about the activity of β-lactam compounds against gram-negative bacilli? With the fermentation product 6-aminopenicillanic acid as a starting point (figure 1, top), major changes in the side chain (R) of the penicillin G molecule were necessary over the last decades to expand the antimicrobial spectrum of the β-lactam compounds to include the common gram-negative enteric organisms. It must be remembered, however, that these compounds, which are mostly ampicillin analogues and esters (table 1), exert their activity at concentrations often 10–100 times higher than those of penicillin G. This observation is even more striking when one considers the newer α-carboxylpenicillins and acylamino analogues of ampicillin—notably, carbenicillin, ticarcillin, azlocillin, and piperacillin—which are characterized biochemically by further modifications of the side chain and bacteriologically by their expanded spectrum, including many *Pseudomonas* species, at the cost of very high MICs.

In striking analogy with the penicillins, a variety of semisynthetic derivatives of the closely related compound cephalosporin C and its nucleus (figure

Table 1. Modifications of the penicillin G molecule for production of representative penicillins with an expanded activity against gram-negative bacilli.

	Modification		
Antibiotic	Side chain (R)*	β-Lactam ring	Thiazolidine ring
Ampicillins	α-Amino-benzyl-	No	No
Carbenicillins	α-Carboxyl-benzyl-	No	No
Ureidopenicillins	Acyl-ureido-	No	No
Piperacillin	Piperazine-amino-benzyl-	No	No

* See figure 1 for location of R.

Table 2. Modifications of the cephalosporin C molecule for production of representative first-, second-, and third-generation cephalosporins.

Antibiotic group, examples	Modification			
	Side chain*			
	R1	R2	β-Lactam ring	Dihydrothiazine ring
First generation				
Cephalothin, cephapirin, and cephalexin	Yes	Yes	No	No
Second generation				
Cefamandole, cefazolin, and cefuroxime	Yes	Yes	No	No
Cefoxitin	No	Yes	Yes	No
Third generation				
Cefotaxime, cefsulodin, and cefoperazone	Yes	Yes†	No	No

* See figure 1 for location of R1 and R2.
† Large heterocyclic side chain.

1, bottom), 7-aminocephalosporanic acid, has been developed. The first- and second-generation cephalosporins are characterized biochemically by modifications of both side chains (R1 and R2), with the exception of cefoxitin [6, 7]. These later cephalosporins differ among themselves by minor variations in antibacterial spectrum and pharmacokinetic properties (table 2). Third-generation cephalosporins still contain the 7-aminocephalosporanic acid nucleus, but it is now flanked by two expanded, heterocyclic, bulky side chains. These newer modifications have resulted concomitantly in an impressive expansion of the antibacterial spectrum to include commonly resistant, often nosocomial, gram-negative organisms, as well as in a dramatic decrease in the MICs of the drugs for most of the gram-negative organisms.

Research in the field of β-lactam compounds has led to other recent interesting developments. First, the question can be asked whether the integrity of the thiazolidine ring is a prerequisite for antibacterial action or interaction with bacterial substrates. That this integrity is not necessary is shown by the compound clavulanic acid and its many derivatives—short-chain β-lactams that have the S atom of the thiazolidine ring replaced by an O atom and have little antibiotic activity but possess potent inhibitory effects on most of the microbial β-lactamases (table 3). Olivanic acid derivatives—i.e., penicillin analogues in which the heterocyclic S atom has been replaced by a C atom—are another interesting group of β-lactamase inhibitors. Thienamycin and its derivatives are chemically related to the olivanic acids, but the former exhibit strong antibacterial activity against a large variety of gram-negative and gram-positive, aerobic and anaerobic organisms. Newer synthetic compounds also include sulfone derivatives of penicillanic acid, a group of potent irreversible inhibitors of β-lactamases. Last but not least, moxalactam represents probably the boldest modification of the initial β-lactam structure, which produced a combination of chemical and microbiologic properties found individually in many of the various β-lactam compounds presently available. It is of great interest to note that the MICs of these new compounds for certain gram-negative organisms are in the range of those reported 50 years ago with penicillin G for suscep-

Table 3. Modifications of the β-lactam structure for production of new β-lactam antibiotics and related compounds.

Antibiotic or compound	Side chains	Modifications in	
		β-Lactam ring	Thiazolidine ring
Clavulanic acid and derivatives	Short	No	S replaced by O
Olivanic acid and derivatives	Variable	No	S replaced by C
Thienamycin and derivatives	Variable	No	S replaced by C
Penicillanic acid and derivatives	Absent	No	S replaced by sulfone
Moxalactam and derivatives	Large	No	Dihydrothiazine ring; S replaced by O

tible gram-positive organisms. By analogy, one can therefore conclude that it will be difficult to improve the antibacterial activity of such compounds against gram-negative organisms. If proved effective in clinical trials, these compounds could well simplify our future approach to antibacterial therapy for hospital-acquired infections.

Assessment of the Biological Activities of β-Lactam Compounds

Antibiotic activity is customarily expressed either in terms of MICs and MBCs in an in vitro microbiologic system or in terms of efficacy in an experimental animal model. Extrapolation from such data to infections in humans is not always possible and is often conceptually incorrect because a variety of biophysical, microbiologic, and specific host factors, which are operative during infections, are not adequately assessed by these conventional susceptibility studies or may show important variations from species to species. Finally, we still do not know how bacteria are killed by antibiotics in the human host, whether host defense mechanisms are potentiated when in contact with altered bacteria, and whether locally persisting bacteria will be recognized and eliminated by the host immune system.

Fortunately, more refined measurements of antimicrobial activity and exciting new discoveries allow us now to put into proper perspective some events that are induced by these compounds and occur prior to microbial death. As we shall see, these events can now be recognized and followed by biochemical and morphologic techniques and might by themselves alter the handling of the "sick" microorganism by the host. For instance, a refined view of the mode of action of some β-lactam compounds has emerged through the demonstration of their protein-binding sites at the cell membrane level [8] and of their induction of morphologic changes in susceptible bacteria [9]. These modifications, observed either in specific intracellular structures or at the cell membrane level before or concomitant with the first expression of their antibacterial activity, can be used, among other approaches, as new screening tests for novel antibacterial compounds.

Along the same line of thought, evidence is accumulating that within the human body concentrations of an antibiotic too low to kill microorganisms might still render them more susceptible to nonspecific or specific host clearance mechanisms. This concept emerges from several studies with subinhibitory concentrations of antibiotics defined so far by morphologic criteria, turbidimetry, time-killing curves, synergistic studies, or by determination of the recovery period after exposure to antibiotic [10–12]. Because β-lactam derivatives primarily alter the bacterial cell wall structure at subinhibitory concentrations, it follows that bacteria exposed to minimal amounts of antibiotics will present an altered surface to the host, and therefore a modified relation between these two types of cells is produced. Thus, bacteria exposed to subminimal concentrations of β-lactam or other antibiotics show suppressed adherence to human cells, decreased mannose-binding activity, decreased binding to uroepithelial cells, and increased engulfment by phagocytic cells [10–12]. Several of these mechanisms are presently believed to be important pathogenic factors in human disease. If indeed the pathogenicity of the organisms and/or their handling by the host can be altered by such compounds at concentrations that are imperceptible by conventional microbiologic techniques, new light will be shed on basic questions such as the blood and tissue levels of antibiotic that are required to control infection. These observations might also help to develop new compounds that alter the binding of potential pathogens to mucosal surfaces or phagocytic cells without exerting an antibacterial effect on the physiologic flora of the host, which is another way to treat or prevent infection.

Conclusions

The history and the present state of the β-lactam antibiotics look impressive; so does the future. Whereas little is to be expected from the development of new compounds even more active against gram-positive non-β-lactamase-producing organisms, there is a need for new antibacterial substances that show better bactericidal activity against β-lactamase-producing gram-positive organisms and particularly against gram-negative bacilli. The potency of present and future compounds against most gram-negative organisms will probably reach the levels described by Fleming [2] for penicillin G, at the expense of a loss in their

antimicrobial spectrum against gram-positive organisms. Finally, it is conceivable that new compounds of the β-lactam group, used at low concentrations, may alter the bacterial surface of pathogens to render them more susceptible to antibacterial clearing mechanisms in humans. Just by following these two lines of thought, I suspect that we have many years of exciting basic and clinical research ahead of us.

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