antimicrobe Drugs

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Penicillins

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INTRODUCTION

In 1929, Alexander Fleming isolated penicillin from a strain of *Penicillium notatum* (84). By 1941, benzylpenicillin could be produced in sufficient quantity to treat several infected patients. Clinical trials with the agent, conducted by Florey and colleagues, were successful and during World War II, benzylpenicillin was used to treat patients with streptococcal, gonococcal, and treponemal infections. Shortages of the agent continued until the late 1940s when production of large amounts of drug became possible by a deep-fermentation procedure (85). Since then, many synthetic penicillins have been developed, but resistance to the agents has increased. Despite the emergence of resistance to penicillins and the development of other classes of anti-infective agents, the penicillins remain one of the most important anti-infective classes of drugs well into the nineties. In fact, penicillin G is still the drug of choice for many types of infections, including syphilis and certain types of endocarditis.

CLASS

Chemical Structure (Figure 1)

The basic chemical structure of all penicillins consists of a beta-lactam ring, a thiazolidine ring, and a side chain (6-aminopenicillanic acid). The antibacterial activity of the penicillins lies within the beta-lactam ring. Any alteration in this ring structure forms penicilloic acid and the antibacterial activity of the compound is lost. The side chain varies with each penicillin compound and generally determines the spectrum of activity, as well as the pharmacokinetic properties of the compound. There are several natural penicillins (penicillin dihydro F, X, and K), of which benzylpenicillin (penicillin G) is the most active and is the only natural penicillin used clinically (164).

Structure-Activity Relationships

Manipulations of the side chain have produced compounds that are stable against certain bacteria, such as *Staphylococcus aureus*, which produce beta-lactamase enzymes (penicillinase). The side chain sterically inhibits the beta-lactamase hydrolysis of the beta-lactam ring. Other penicillin compounds have side chains, which are stable against beta-lactamases produced by gram-negative rods. Side chain changes can also increase the bacterial permeability of the compound and can result in increased oral absorption from the intestinal tract by rendering oral agents more stable to gastric acid breakdown (167, 186).

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ANTIMICROBIAL ACTIVITY

Classification of Penicillins and Spectrum of Activity

The penicillin compounds can be divided into categories based upon their spectrum of activity (Table 1). Minimum inhibitory concentration (MIC) data for 50% and 90% of specific organisms are located in Tables 2 and 3 (10, 70, 156, 228, 245, 255, 257, 261). For gram-negative organisms and anaerobes, resistance in up to 15% of strains is possible; therefore MIC90s must be interpreted cautiously.

Natural Penicillins

Penicillin G is a natural penicillin that is produced directly from fermentation of *Penicillium crysogenum*. Penicillin V is a derivative of penicillin G and because of similarities in spectrum of activity, is considered a natural penicillin. The natural penicillins have activity against non-beta-lactamase producing gram-positive cocci, including viridans streptococci, group A streptococci, *Streptococcus pneumoniae*, and anaerobic streptococcus (*Peptostreptococcus*, *Peptococcus* sp.). *Enterococcus* sp. is most susceptible to the natural penicillins. Other potential organisms with susceptibility include non-penicillinase producing strains of *Staphylococcus aureus* and coagulase-negative *Staphylococcus*, however because of the high likelihood of resistance, it is inappropriate to use natural penicillins as empiric treatment for a suspected *Staphylococcal* infection unless the organism's susceptibility is known. The natural penicillins have activity against Clostridium sp. (excluding *Clostridium difficile*) and *Actinomyces* sp. Activity against gram-negative cocci is limited and includes *Neisseria meningitidis*, non- penicillinase producing *Neisseria gonorrheae*, and *Pasteurella multocida*. Similar to *staphylococcal* infection, natural penicillins should not be used for treatment of gonorrhea due to the increased

potential of a resistant organism and subsequent treatment failure. The anaerobic coverage of penicillin V is less than that of penicillin G. Natural penicillins also have excellent activity against the spirochete, *Treponema pallidum*, the causative organism of syphilis.

Penicillinase-Resistant Penicillins

The agents in this group are also known as the antistaphylococcal penicillins. The addition of an isoxazolyl side chain to the penicillin compound protects the beta-lactam ring from acid hydrolysis by penicillinases produced by *Staphylococcus* sp. (150). Methicillin, the first agent synthesized in this group, is rarely used currently due to a higher incidence of occurrence of interstitial nephritis and is no longer commercially available in the United States. Nafcillin and oxacillin are the agents commonly used parenterally, while dicloxacillin is available for oral use. These agents have activity against *Staphylococcus* sp (including penicillinase-producing strains). Strains of methicillin-resistant *Staphylococcus aureus*(MRSA) and methicillin-resistant *Staphylococcus epidermidis* (MRSE) exist and can be the prevalent *Staphylococcal* organism in certain areas, such as certain hospitals or wards within the hospital. These organisms are not sensitive to the penicillinase-resistant penicillins.

While less active against streptococcal sp. as compared to the natural penicillins, based on MIC data, use of the penicillinase-resistant penicillins is acceptable (i.e. the MICs are low enough relative to achievable serum concentrations) for use against these organisms. Clinically, in serious, life-threatening infections where a gram-positive organism is suspected, combinations of penicillin G plus a penicillinase-resistant penicillin can be utilized to achieve maximal streptococcal and *staphylococcal* coverage. A notable exception to the gram-positive coverage of this class of penicillins is the Enterococci. These organisms are not susceptible to this class of penicillins. Anaerobic activity ranges from minimal to none and gram-negative activity is virtually nonexistent.

Aminopenicillins

Because of the need for improved coverage against gram-negative organisms, further manipulation of the side chain was conducted. By adding an amino group to the basic penicillin compound, the aminopenicillins were developed. The spectrum of activity against gram-positive organisms is similar to that of the natural penicillins. These agents retain activity against streptococcal sp. and have slightly greater activity against *Enterococcus* (ampicillin) and *Listeria monocytogenes* versus the natural penicillins. The added side chain does not, however, inhibit hydrolysis by *Staphylococcal* penicillinases or gram-negative beta-lactamases. The enhanced spectrum of these drugs includes activity against gram-negative bacilli including *H. influenzae*, *E. coli*, *Proteus mirabilis*, *Salmonella* sp., and *Shigella* sp. (13, 83). These drugs were developed in the 1960s and were, at that time, very effective against these organisms. Presently, however, many strains of these gram-negative organisms are resistant to ampicillin. Combinations of an aminopenicillin plus a beta-lactamase inhibitor, such as clavulanic acid or sulbactam, are useful for treatment of infections caused by beta-lactamase producing organisms.

Carboxypenicillins

A carboxyl group substitution in place of the amino group yields penicillin compounds that have a greater gram-negative spectrum of action, including activity against *Pseudomonas aeruginosa*, most likely due to increased bacterial penetration through the cell wall. Carbenicillin and ticarcillin are the two drugs in this class. Their spectrum of activity includes that of ampicillin, while also encompassing *Enterobacter*, *Providencia*, *Morganella*, indole-positive *Proteus*, and *Pseudomonas aeruginosa*, with ticarcillin having slightly greater activity against *Pseudomonas aeruginosa* versus carbenicillin (19). Coverage against *Klebsiella* and *Serratia* are less predictable and, unlike ampicillin, these compounds have little activity against *Enterococcus*. These agents are not effective against beta-lactamase producing organisms unless combined with a beta-lactamase inhibitor (e.g. ticarcillin plus clavulanic acid).

Ureidopenicillins and Piperazine Penicillin

In order to increase gram-negative coverage and particularly coverage against *Pseudomonas aeruginosa*, a ureido group addition to the penicillin structure produces the compounds azlocillin and mezlocillin. A ureido group plus a piperazine side chain produces piperacillin. The gram-negative coverage of this class of penicillins includes that of the carboxypenicillins, plus coverage against *Klebsiella*, *Serratia*, *Enterobacter*, *Enterococcus*, and increased anaerobic coverage (228). The activity against Streptococci is slightly less that of the natural penicillins and ampicillin. Of the drugs in this class, piperacillin has the most activity against *Pseudomonas aeruginosa* (52, 255). As with the carboxypenicillins, drugs in this class are susceptible to inactivation by bacterial beta-lactamase production, unless combined with a beta-lactamase inhibitor (e.g. piperacillin plus tazobactam).

Pharmacodynamic Effects

When choosing an antimicrobial agent and designing appropriate dosing regimens for the drug, it is important to consider spectrum of activity, but also incorporate known pharmacodynamic principles about the drug. In this manner, efficacy can potentially be maximized while toxicity can be minimized. Some excellent reviews on these concepts have been published (71, 76). Such pharmacodynamic variables that are important to consider for the penicillins includes concentration-independent bactericidal activity, the post-antibiotic effect (PAE), and the duration of the dosing interval the drug's serum concentrations spend above the level of the organism's MIC (Time > MIC).

Bactericidal Effects

All beta-lactam drugs (including the penicillins) exert relatively concentration-independent bactericidal activity, meaning that the concentration of drug does not appreciably affect its ability to exert an antibacterial effect (25, 209). This assumes, however, that a level that exceeds the organism's MIC is attained. Theoretically, the bactericidal rate at 2 times above the MIC or 4 times above the MIC would be the same. However, once the drug concentration falls below the level of the MIC and the PAE has ceased, the kill rate diminishes. Time > MIC is therefore the important determinant of outcome for these drugs.

A paradoxical phenomenon of decreased effect with higher drug concentrations, known as the "Eagle effect", has been described with some strains of streptococci and staphylococci (111). This effect, however, does not appear to be clinically significant, as there is very limited data to support decreased bactericidal activity *in vivo* due to high serum concentrations.

Another factor that may influence bactericidal activity is bacterial inoculum size. Generally, the more dense the bacterial population (i.e. the older the infection), it is more likely that there will be resistant variants of the organism present. This may be the case with nosocomial gram-negative pneumonias or other serious infections. Treatment with a penicillin as monotherapy may result in a relapse after completion of therapy when the resistant sub-variants are no longer suppressed and begin to regrow. This scenario is not unique to the penicillins, and in fact may occur with other antibiotics when used as monotherapy.

The bactericidal activity of the penicillins does not appear to be affected by changes in pH or oxygen tension. The location of the organism is important, however, as *in vitro* efficacy may not correspond to *in vivo* efficacy. Penicillins and other beta-lactams do not penetrate well into phagocytes (104), thus limiting their ability to kill intracellular pathogens. In addition, penicillins only exert their bactericidal effect on bacteria that are actively replicating.

Synergistic Bactericidal Activity

Combinations of a beta-lactam plus another agent, such as an aminoglycoside, kill some organisms most effectively. In these cases, antibacterial synergy occurs. Synergy is defined as an effect, such as bactericidal activity, that is significantly greater with the combination than the sum of the two agents when used alone. The mechanism of this effect with penicillins and aminoglycosides may be due to cell wall disruption by the penicillin, facilitating increased entry of the aminoglycoside into the bacteria (158). Enterococcal endocarditis is such an example, as penicillin monotherapy results in bacteriostatic activity and very high relapse rates after treatment (149), while the combination of penicillin plus an aminoglycoside is bactericidal (157).

Other organisms for which synergy seems to be important with regard to the penicillins includes *Pseudomonas aeruginosa*. Again, a combination of an antipseudomonal penicillin plus an aminoglycoside may result in increased bactericidal activity. This has been demonstrated *in vitro* and animal studies (9, 77, 118), but there is limited data in humans to support these findings. *In vitro* synergy between the extended spectrum penicillins (azlocillin, mezlocillin) and ciprofloxacin has also been demonstrated (152, 178, 225). Immunocompromised patients are a population who may benefit the most from antipseudomonal synergy. There is data to suggest that synergistic combination therapy results in increased survival versus non-synergistic combinations of drugs (124, 130, 204).

Antagonism of Antibacterial Combinations

Antibacterial antagonism is defined as a resulting effect that is significantly less in combination than with either of the two drugs when used as monotherapy. This effect has been demonstrated with the penicillins in combination with chlortetracycline in patients with pneumococcal meningitis, when penicillin monotherapy was more effective that the combination of agents (133). Combinations of penicillin plus chloramphenicol have demonstrated *in vitro* antagonism against pneumococci (188), however, clinically this may be of little importance since the combination only diminished penicillins bactericidal activity (resulting in bacteriostatic activity) and chloramphenicol retains its antibacterial effect. Also, the use of chloramphenicol has decreased dramatically in the last decade due to the availability of newer agents that are equally efficacious and less toxic.

Antagonism can also occur due to a physical incompatibility with inactivation between two drugs when infused together. This can occur with carbenicillin or ticarcillin with an aminoglycoside. These drugs should therefore not be mixed in the same infusion.

Post-Antibiotic Effect

The PAE is defined as a persistent suppression of bacterial growth after effective exposure to an antimicrobial agent when serum concentrations of the drug have fallen to levels below the MIC. This effect differs between infecting organisms and between drugs. The mechanism of the PAE is not entirely clear, but may be due to persistent binding of the penicillin to penicillin-binding proteins (PBPs) and the time that is necessary for the organism to resynthesize new PBPs (218).

The PAE was first noted with penicillin G and *Staphylococcus aureus* (179), when it was noted that there was a short period of time where bacterial regrowth did not occur after exposure to the drug. Subsequently, this phenomenon has been described with the penicillins for other gram-positive organisms (42, 108), including *Streptococcus pneumoniae* and*Enterococcus faecalis*. The length of the PAE can range from 0-6 hours (Table 4), depending upon the penicillin.

As stated previously, the type of organism can affect the PAE. The penicillins do not exhibit an appreciable PAE against gram-negative organisms. Also, combinations of antimicrobial agents can result in a synergistic PAE. Combinations of penicillins plus various aminoglycosides have resulted in synergistic or additive PAEs for *Enterococcus faecalis* and*Enterococcus faecium* (85, 108), along with *Staphylococcus aureus* (100).

Models of Antibacterial Outcome Determination

Bactericidal activity of penicillins and other beta-lactams appears to be related to the Time > MIC, as demonstrated in several *in vitro* models. A number of studies of beta-lactam agents demonstrated that increased half-life and not peak concentration influenced bactericidal activity (97, 125, 254, 272). This implies that increased duration of drug exposure above the MIC would be more predictive of positive outcome versus increased drug doses and subsequent increased peak concentrations.

Data from animal models supports Time > MIC as the primary determinant of efficacy for beta-lactam agents (75, 247). In a neutropenic mouse model infected with *Pseudomonas aeruginosa*, the impact of different dosing intervals of ticarcillin was studied. Equivalent daily doses were administered every hour or every 3 hours. The mice that received drug every hour (a lower dose