PHARMACEUTICAL AND BIOLOGICAL EVALUATIONS
December 2017; Vol. 4 (Issue 6): 234-238.
www.onlinepbe.com
ISSN 2394-0859

Review Article

DOI: http://dx.doi.org/10.26510/2394-0859.pbe.2017.36

Cephalosporins: pharmacology and chemistry

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Received: 05 November 2017
Revised: 28 November 2017
Accepted: 30 November 2017

ABSTRACT

Cephalosporins are the most important antibiotics having β-lactam ring and are obtained from a fungus Acremonium, also known as cephalosporium. The wide use of cephalosporins against bacteria in various severe infections such as respiratory tract infection (RTI), skin infection and urinary tract infection (UTI) has led the scientist dive into the detail of this antibacterial drug. The knowledge about structural activity relationship (SAR), spectrum of inhibition (SOI), chemical properties and pharmacology of cephalosporin has pivotal impact to device advanced therapeutic results. The treatment of a disease using cephalosporin has many pros and cons. If the pharmacology and chemical properties of this drug are known properly, many side effects can be diminished or minimized to a certain level. This article review some pharmacological and chemical properties of cephalosporins.

Keywords: Cephalosporin, Antibiotics, Pharmacology, Cefixime, β-Lactams

Introduction

Cephalosporin compounds were first isolated from cultures of *Cephalosporium acremonium* from a sewer in Sardinia in 1948 by Italian scientist Giuseppe Brotzu. Cephalosporins are obtained naturally from cephalosporin C that is obtained from a fungus *Cephaosporium acremonium*.[1] Chemically they are derived from 7 aminocephalosporic acid and they are structurally and functionally related to penicillins because they shared a common β- lactam ring. Cephalosporins are composed of a six membered ring having sulfur atom attached to a β-lactam ring. Cefixime comes under third generation semisynthetic β-lactam antibiotic of cephalosporin group. Cefixime has molecular weight 453.4 and has molecular formula $C_{16}H_{15}N_5O_7S_2$.[2] Cefixime is marketed in the form of tablets and suspensions only for oral use.[3]

Properties of cephalosporins

Cephalosporins have very simple pharmacology as compared to other agents. Most of the cephalosporins are in parenteral form, have short half-life (1-2 hours). Their excretion occurs through urine. Some agents have long half-life such as ceftriaxone and excretion occurs through bile. The microbiology is complicated and is linked with three factors. Stability to β-lactamases is a key factor. The development of cephalosporins stemmed from the stability of cephalosporin C to staphylococcal beta-lactamases and this property is present in all cephalosporins. Stability to beta-lactamases of Gram-negative enterobacteria is variable even

with transferable beta-lactamases and some compounds show increased stability to class C enzymes. Finally there are the cephalosporinases of anaerobic gram-negatives to which a few cephalosporins are stable. The ability to penetrate the outer membrane of a gram-negative rod is another key factor in the activity against many organisms e.g. pseudomonads and this property also varies.[4]

Classification of cephalosporins

A method for classification of cephalosporins on the basis of microbiology and pharmacology was devised a few years ago. On the basis of microbiology cephalosporins are placed into four major groups given below

Cefazolin is highly effective against many strains of *E.coli*, cefoperazone undergoes hydrolysis by some enzymes such as transferable beta-lactamases and cefotaxime undergoes deacetylation in vivo, protein binding of ceftriaxine is very high and has longest half-life. Classification on the basis of science is too informative as compared to generations. Cephalosporins fall practically into four major classes.

I. Increased activity against Gram-positive bacteria: cephalothin, cefazolin

II. Increased activity against enterobacteria and parvobacteria

- **a.** Cefuroxime, cefamandole
- **b.** Cefotaxime, ceftriaxone
- **c.** Cefepime, cefpirome

III. Increased activity against *Enterobacteria*, *Parvobacteria* and *Pseudomonas* spp: ceftazidime, cefoperazone

IV. Increased activity against *Enterobacteria* and *Bactericides*: cefoxitin, cefotetan

Cephalosporins can also be classified on the basis of chemical structure:

Glycyl-cephalosporins: (Cefaclor, cefadroxil, cephalexin, cefprozil and loracarbef). The good absorption of glycyl-cephalosporins is mostly independent of food intake and based upon the existence of a specific carrier system similar to that of natural dipeptides. Because of this mechanism, relatively high serum levels are attained. Another advantage of the glycyl cephalosporins is the lack of taste of the pure substance. This is the prior condition for the preparation of pleasant tasting syrup.

Aminothiazole-/oxime-cepha*:* (Cefixime, ceftibuten, cefetamet, cefopodoxime). The aminothiazole-oxime-cephalosporins are derived from the structure of cefotaxime, which accounts for their broad activity cephalosporins.

Prodrug cephalosporins: (Cefuroxme axetil, cefopodoxime axetil, cefetamet pivoxil) prodrug cephalosporins are esters, that are already hydrolysed after resorption in the small intestinal mucosa. The bioavailability of prodrug cephalosporins can be improved by food intake. The bitter flavor is a disadvantage, which cannot be completely eliminated even in aromatic syrup mixtures[4].

Systematic (IUPAC) name

Chemically its name can be represented as (6R, 7R)-7-{[2-(2-amino-1, 3-thiazol-4-yl)-2-(carboxymethoxyimino) acetyl] amino}-3-ethenyl-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2 carboxylic acid.[5]

Structure activity relationship

Chemically it is composed of a cephem nucleus that is attached to a six membered ring of dihydrothiazine. At position 3, cephem nucleus has a vinyl group for the absorption of intact molecule through intestine and at 7-position acetic acid oxy-imine group and aminothiazole ring are attached for antibacterial activity. Its structure is shown in figure as below.[6]

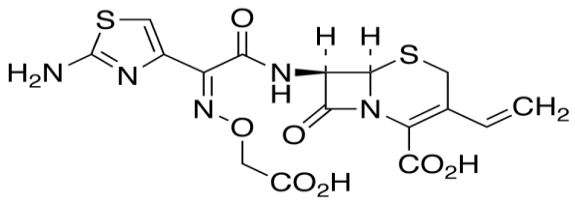

Figure 1: Chemical structure of cefixime.

The ring structure of cephalosporin is derived from 7-aminocephalosporanic acid (7- ACA) and contains the basic beta-lactam ring. Modification of the 7-ACA side chains resulted in the development of potent and useful antibiotic agents, and the first agent cephalothin was launched in 1964. The cephalosporin nucleus can be modified to gain different properties. Various groups can be added to the beta-lactam ring or dihydrothiazine ring that can change the activity and pharmacokinetic properties. Although used as broad spectrum antibiotic, cephalosporin are not effective against all the bacteria commonly isolated in a hospital microbiological laboratory. Organisms that are not inhibited by cephalosporins consequently overgrow with varying potential to cause infection. It is therefore, important to design newer cephalosporin with better activity and favorable pharmacokinetics. This shows an extreme need of further research for each drug type in the classification of cephalosporins. It was observed from mathematical models that parameters of activity of drug were highly associated with its lipophilicity and presence of sulfur or oxygen atom at a specific position. The presence of sulfur or oxygen atom and increased lipophilicity was observed to increase activity of drug. Moreover, compounds with molecular weight less than 600 hundred and minimum 10 hydrogen bond acceptor were associated to increase activity. It was also observed from mathematical model that parameters of pharmacokinetic studies (half-life, clearance and fraction bound) were highly linked with lipophilicity of cefixime. Previously, physical chemists recognized that biological activity of compounds is associated with its structure, physical and chemical features. These studies led to the development of quantitative structure activity relationship.[7]

Mechanism of action

Cell wall of bacteria is made up of sequence of repeating and interlocking units of floor tiles. During its replication a bacterium removes tiles circumferentially to permit division of cells through an action like pinching and quickly place tiles at the end of division in to two bacteria. This action needs enzymes to interconnect replacement tiles. These enzymes are targeted by antibiotics of beta lactam group and are known as penicillin binding proteins. Antibiotics bind to penicillin binding proteins and prevent them from closure the ends of dividing bacteria and increase hyper osmotic pressure to kill the bacteria.[8] Cephalosporins are bactericidal and have the same mode of action as other beta-lactam antibiotics; such as penicillins. The peptidoglycan is an important substance for cell wall structural integrity. Cephalosporins disrupt the synthesis of the peptidoglycan layer of bacterial cell walls by binding to enzymes called penicillin binding proteins (PBPs). These enzymes are essential for the synthesis of the bacterial cell wall.[7]

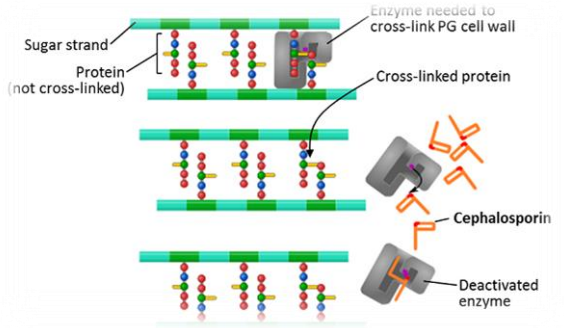

Figure 2: Mechanism of action of cephalosporins.

Cefixime inhibited the multiplication of bacteria by interfering with the synthesis of cell wall. Cell wall is an integral part of bacterial structure that helps the bacteria in survival under unfavorable conditions from environment. Without cell wall bacteria are susceptible to environment and could die. Cefixime also performs its lytic action rapidly against pathogens by binding with penicillin-binding proteins that are present in cell wall.[9]

Bacterial resistance mechanisms

β-lactam antibiotics interact with penicillin binding proteins in susceptible pathogens. Each strain of bacteria has different types of penicillin binding proteins. Gram negative bacteria have different varieties of penicillin binding proteins (PBP) than gram positive bacteria. Mutations in PBPs can reduce the penetration of antibiotics having β-lactam ring for certain bacteria. An

excessive concentration of drug is essential to inhibit growth of such type of bacteria. Higher concentrations of drug must be available in proximity of mutated PBPs to inhibit bacterial growth. In acute infections of ear caused by penicillin-non-susceptible Streptococcus pneumonia (PNSP), higher doses of drug (amoxicillin) are needed. Another common way for the development of resistance is the formation of beta-lactamase that causes the breakdown of beta-lactam ring. It inhibits antibiotic to react with PBPs. TEM-1 β-lactamase is an example of Non-typeable Haemophilus influenza which is responsible for ineffectiveness of cefaclor and cefprozil.[8]

Spectrum

The cephalosporins are divided into three groups according to their antibacterial spectrum. Recently the first generation compounds that is available for parenteral use (cephalothin, cephapirin, cephazolin) and for oral use (cephadroxil, cephradine and cephalexin). All of these groups of antibiotics are parallel in spectrum. They are less active against gram negative bacteria. Although several strains of *Klebsiella*, *Proteus mirabilis* and *E.coli* species are sensitive. They have no activity against methicillin-resistant *Staphylococus epidermidis* and methicillin-resistant *Staphylococus aureus*, *Bacteroids fragalis, Enterococci, Listeria mnocytogenes, Proteus* other than *mirabilis, enterobacter, pseudomonas, Serratia* and *propvidencia* organisms. Gram positive microorganisms (anaerobes) such as non β-lactamase producing species of *Bacteroids* and *Peptostreptococcus* are particularly susceptible.

The second group of cephalosporins are cefonicid, cefamandole, and ceforanide. Cefotetan, cefoxitin and cefmetazole are incorporated in this group. These compounds are technically considerd cephamycins due to the presence of methoxy group at C_7. Cefuroxime axetil and cefaclor are the only second generation group of cephalosporins administered orally. These antibiotics are generally active against the same group of organisms like first class of cephalosporin. They are more effective against Haemophilus influenza and certain gram negative aerobic bacteria. Cefaclor has generally limited activity against gram negative microbes than the other compounds. *In vitro* studies using cefotetan and cefmetazole showed slightly less activity against species of *bacteroids* than cefoxitin. However, the second generation agents, cefmetazole, cefamendole and cefuroxime have limited activity against staphylococci than the first group of cephalosporins. Second generation agents of cephalosporins are not active against L. monocytogenes, *enterococci*, Methicillin-resistant *Stapylococcus epidermidis*, Methicillin resistant *S.aureus*. Cefotetan has more activity against gram negative aerobic bacilli than the second generation compounds.

Third generation cephalosporins consist of cefotaxime, cefoperazone, ceftazidime, ceftizoxime and moxalactam ceftriaxone. Cefixime has greater advantage over other cephalosporins that used orally due to its remarkable stability to β-lactamase and its extensive coverage against gram negative bacteria. It has a meager activity against staphylococci and only marginal activity against pneumococcal bacteria. The third generation agents of cephalosporins (parentaral agents) have less activity against staphylococcus bacteria but extended activity against gram negative bacteria. Cefotaxime and ceftizoxime show its activity against *Bacteroid fragilis* and other anaerobic microorganisms. Ceftazidime and cefoperazone are the only agents of cephalosporins that contain reliable effectiveness for Psudomonos aeroginosa. Third generation cephalosporins along with first and second generation agents do not show activity against Listeria monocytogenes, MRSE, MRSA and *Enterococci*.[10]

Conclusions

The structural activity relationship (SAR), chemical and other pharmacological properties of cephalosporins have categorized this class of antibiotics as the most important penicillin binding protein (PBP) targeting drug. The cefixime is the drug of choice among all other cephalosporins principally due to its integrity to β-lactamase. However the remarkable coverage

of this class of antibiotic against gram negative bacteria outweighs the other antibiotics against similar bacteria. In depth study of chemical and pharmacological properties of cephalosporins multiplies their advantages for patients in the healthcare system. Pharmacology of a drug alters by genetic and environmental factors which is a new line for future research and the effect is known as pharmgeonetics.[11]

Funding: No funding sources
Conflict of interest: None declared

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