CEPHALOSPORINS

The first source of Cephalosporins → "Cephalosporium acremonium."

↓

Isolated in 1948 by BROTZU from sewer outlet off the Sardinian coast

Cultures of fungus

↓

found to inhibit growth of S. aureus in vitro to cure Staphylococcal and Typhoid fever in Humans.

These Sardinian fungus → three distinct antibiotics.

Cephalosporin P, N and C.

Active nucleus of Cephalosporin C → 7-amino cephalosporanic acid.

↓

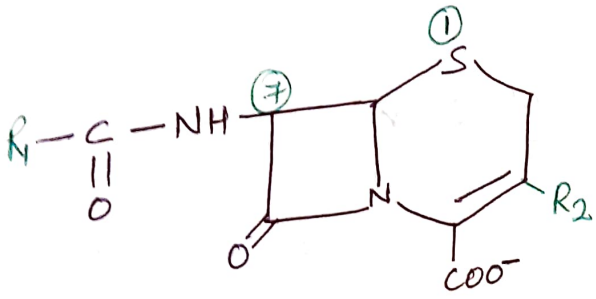
addition of side chains

↓

Semisynthetic compounds

↓

with antibacterial activity greater than parent substance.



CEPHEM NUCLEUS

dihydrothiazine ring attached to β-lactum ring. Changes in (7) → diff. spectrum of activity

(3) → diff. P. kinetics.

classification is based on "generations".

None of the Cephalosporins have activity against MRSA, Listeria or Enterococci. Classification based on general features of antimicrobial activity.

Classification :→

I. FIRST GENERATION : →

ORAL :

CEPHALEXIN

CEPHARADINE

CEPHADROXIL

PARENTRAL

CEPHALOTHIN (discontd. in US)

CEPHAZOLIN

CEPHALORIDINE

II. SECOND GENERATION : →

ORAL

CEFACLOR

CEFUROXIME AXETIL

CEFPROZIL

PARENTRAL

CEFUROXIME

CEFOXITINE

CEFAMANDOLE

III. THIRD GENERATION : →

ORAL

CEFEXIME

CEFPODOXIME PROXETIL

CEFDINIR

PARENTRAL

CEFOTAXIME

CEFTIZOXIME

CEFTRIAXONE

CEFTAZIDIME

CEFAPERAZONE

CEFTIBUTEN

IV. FOURTH GENERATION : →

PARENTRAL

CEFEPIME

CEFPIROME

Antibacterial spectrum :→

I generation → good activity against gram +ve bacteria and relatively modest activity against gram -ve microorganisms

Most of gram +ve cocci except MRSA, Enterococci & S. epidermis all others are suceptible, including oral cavity anaerobes.

Resistant strains :→ B. fragillus, Moraxella catarrhalis E.Coli, K. pneumoniae & P. mirabilis

II generation :→ increased activity against gram -ve microorganisms but are much less active than the third-generation agents.

active against B. fragillus, H. influenza.

Resistant P. aeuroginosa.

III generation :→ Less active than first generation against gram +ve cocci & much active against gram -ve.

Much more active against Enterobacteriaceae but resistance increased due to β-lactamase producing strains.

~~Ceftaz~~ ceftazidime } active against P. aeuroginosa
cefoperazone } ~~but~~

IV generation :→ Extended spectrum compared with third generation and have increased stability from hydrolysis by plasmid and chromosomally mediated β-lactamases.

Mech. of Resistance :→ Same as penicillins.

→ inability to reach site of action
→ Alterations in PBPs
→ β-lactamases prodⁿ
→ Hydrolysis of cephem rings

Excretion :→

→ 1° excreted by kidneys
∴ dosage adjustment required → Renal insufficiency

→ Probenecid slows tubular secretion of all Cephalosporins.

→ Ceftriaxone and Cefoperazone → excreted predominantly in Bile.

→ Cefotaxime → deacetylated → resultant metabolite has less antimicrobial activity
↓
excreted by kidneys

→ No other compounds undergo appreciable metabolism.

Distribution :→

→ Several Cephalosporins penetrate CSF in sufficient Concⁿ (Ceftriaxone, Cefepime)
→ Cross placental barrier
→ found in high Concⁿ in Synovial, pericardial fluid.

→ Relatively good penetration in aqeous humor but poor in vitreous humor.

→ Cefoperazone, Ceftriaxone → high Conc. in Bile.

Absorption :→ Effective orally and parenterally.

I Generation

Cefazolin Antibacterial spectrum same as I generation except active against some Enterobacter species.

→ Well tolerated after IM/IV administration
→ plasma levels after 1g IM → 64 µg/ml.
→ 85% bound to plasma proteins
→ Most prefered drug due to longer $t_{1/2}$.

Cephalexin given orally.

less activity against penicillinase producing Staphylococci.

oral adm. 500mg → peak plasma 16 µg/ml

Drug is not metabolised and 70-100% excreted in Urine.

Cephradine :→ IIr structure to cephalexin with IIr activity.

Not metabolised after rapid absorption from GIT.

Can be adm. orally, IM/IV.

plasma conc. nearly equivalent after oral / IM/IV administration.

Cefadroxil → parahydroxy analog of cephalexin
orally given. once / bid → UTI.
activity ↓ to cephalexin.

Advarse effects

→ Pain upon IM admn. of Cefalothin
→ Cepharidine, cefaperazine → Diarrhoea
→ Hypersensitivity reactions similar to penicillins
↓
Skin rashes, Anaphylaxis, Angioedema, Asthma, Urticaria etc.
→ Cefaloridine* → Nephrotoxicity
→ Bleeding, Neutropenia, thrombocytopenia,
⇓
Cefoperazone
→ Given with alcohol → Disulfiram like reaction.
like tremors, burning sensation

Cefaperazone + Alcohol = Alcohol + Disulfiram

Cefamandole :→ active against gram -ve organisms
↓
⇒ methyl Tetrazothiomethyl group in 3rd position → adverse effects like:
disulfiram like reaction & hypoprothrombenemia (↓ of Vit. K activity)
⇒ Broad spectrum against Enterobacteriaceae, Proteus, Klebsiella

II Generation :→

Broader spectrum than I generation, active against Enterobacter species, Indole positive proteus species & Klebsiella species.

Cefoxitine :→ It is a cephamycin produced by Streptomyces lactamdurans.

→ It is more active than other I/II generation agents against anerobes especially B. fragillus.

→ It has a special role in the treatment of certain aerobic & mixed aerobic-anerobic infections such as Pelvic inflammatory diseases, and lung abscess.

Cefaclor :→ Used orally. The conc^{n} in plasma after oral admn. is about 50%.

More active against H. influenza, Moraxella catarrhalis

Cefuroxime Axetil :→ It is 1-Acetyloxyethyl ester of cefuroxime.

orally → 30-50% absorption

the drug is hydrolysed to cefuroxime.

cefprozil :→ orally admn. more active than 1st generation against ~~Penicillinase resistant~~ Penicillin sensitive Streptococci, E. coli, P. mirabilis, Klebsiella & Citrobacter.

III generation :→

$t_{1/2}$ → 1-3 hrs.

III generation :→

Cefotaxime :→ has good activity against many gram +ve & −ve aerobic bacteria

→ Resistent to β-lactamase prod. Bacteria.

→ $t_{1/2}$ → 1 hr ; ∴ admn. to be done for every 4-8 hrs, for serious infections.

→ Drug is metabolised invivo to desacetyl cefotaxime which is less active against microorganisms than its parent compound.

→ However, the metabolite acts synergistically with parent compound against certain microbes.

→ Effectively used for Meningitis caused by H. influenza, Penicillin-sensitive S. pneumoniae & N. Meningitidis.

Ceftizoxime :→

less active against S. pneumonike and more active against B. fragillus.

$\frac{1}{2}$ life → 1.8 hrs ⟹ admn. 8 to 12 hrs.

→ A Single dose is effective in the treatment of ~~Urethral~~, ~~Cervical~~, ~~Rectal~~ or ~~pharyngeal~~ Gonorrhoea.

Cefpodoxime proxetil :→ orally admn. drug with actions similar to 4th generation drugs.

More active against Enterobacter & pseudomonas species.

$t_{1/2}$ → 2.2 hrs.

Ceftriaxone :→ activity is similar to that of ceftizoxime & cefotaxime.

$t_{1/2}$ → 8 hrs. ∴ 1/2 daily can be admn.

⇒ 50% of the drug can be recovered in urine. & remaining is excreted through Bile.

⇒ A single dose (125-250 mg) is effective in the treatment of Urethral, Cervical, rectal or pharyngeal gonorrhoea including penicillinase producing M.O.

Cefixime :→ orally admn. drug

⇒ With clinical efficacy to treat UTI, otitis media, pharyngitis & uncomplicated Gonorrhoea.

UTI → E.coli, P.mirabilis

otitis media → H.influenza, S.pyogenes

pharyngitis → S.pyogenes.

⇒ $t_{1/2}$ ⇒ 3-4 hrs ; Excreted in Urine & bile.

⇒ Std. dose 400 mg/day in Adults & adjustment is done for Renal impairment.

Ceftazidime :→ Has excellent activity against pseudomonas & other gram -ve bacteria.

⇒ poor active → B.fragilis

$t_{1/2}$ = 1.5 hrs. ; Not metabolized.

IV generation :→

Cefepime :→

⇒ Stable to hydrolysis by plasmid encoded β-lactamases (TEM1, TEM2 & SHV-1).

⇒ Active against Enterobacteriaceae that are resistant to other cephalosporins.

⇒ Active against fastidious gram -ve bacteria
↓
H. influenza, N. gonorrhoea, N. Meningitidis.

⇒ It is a poor inducer of and is relatively resistant to Type I chromosomally encoded extended spectrum β-lactamases.

⇒ Excreted 100% by Renal route
Excellent penetration to CSF $\frac{1}{2}$ life → 2hrs.

Uses :→

I generation :→

→ Skin & soft tissue infections. by. S. aureus
S. pyogenes

→ Cefazolin → Single dose just before surgery used as prophylactic measure in which skin flora are the likely pathogens.

II generation :→

→ Cefoxitin → prophylaxis in colorectal surgery where intestinal anerobes are involved.

→ used in UTI, RTI & Infections caused by gram -ve anerobic bacteria

→ Cefoxitin & Cefotetan → drug of choice in Intra-abdominal infections, PID, diabetic foot infections.

III generation :→

→ Infections due to Klebsiella, Enterobacteriaceae, H. influenza, proteus

→ Ceftriaxone & Cefotaxime → Treatment of gonorrhoea, & meningitidis

→ Ceftazidine + Aminoglycosides → Meningitis due to P. meningitidis.

IV generation :→

→ against infections caused by Enterobacter, Citrobacter & Serratia