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A REVIEW: CEFPODOXIME PROXETIL (DOXEF. PROXETIL) DISCOVERY, PREPARATION, APPLICATIONS AND COMPARISON WITH CEFPODOXIME-CLAVULANIC ACID IN ACTIVITY

Sahar B. Aljuboori1, Nedaa A. Hameed A. Rahim[2], Anwar A. Tamer[3]

[1]College of Al-Rafiden University- Dept. of Pharmacy-Baghdad-Iraq.
[2,3] College of Pharmacy - Dept. of Pharmaceutical Chemistry Baghdad, University Baghdad-Bab-Almudam- 10001,Iraq
* Corresponding Author. E-mail: Needarahim@yahoo.com

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ABSTRACT

Doxef. Proxetil is a broad spectrum orally administered cephalosporin (CS) of the third generation. This is a pro-drug that has strong antibacterial activity and In vivo deesterified to Doxef. Overall it is well tolerated and Has important therapeutic ability in many severe infections of bacterial. The drug was used in treating respiratory and urinary tract infections, as well as skin structure, acute otitis media, pharyngitis, tonsillitis, etc.. The current assessment explains physical, biological, clinical aspects, preparation and interactions of (Doxef. proxetil) as well as the efficacy of the combination of Doxef. proxetil and potassium clavulanate.

INTRODUCTION

The term (antibiotics) refers to natural components, such as (bacteria or fungi) of different microorganisms. they are capable of inhibiting Certain Microorganisms Production and of killing their cells(Kourkouta L et al. 2017)Present-day development of semi-artificial derivatives, the term (antibiotics) The word "antimicrobials" refers to natural, semi-artificial and synthetic components that have successfully Prevented the spread of microbes which led to apoptosis. In the meantime, hundreds of new antimicrobials were identified with the different mechanisms of action, and it is well known that The most recent arsenal offers full defence against almost all pathogens (Kourkouta Let al. 2018) All Antimicrobials are now commonly used in herbal practice as well as in agriculture, fish farming, cattle breeding, as growth-protective agents oras growth enhancers (Lewis KL et al.2006) Doxef.

Proxetil is a wide spectrum of third-generation (cephalosporin CS) with good antibacterial activity against both Gram-positive (GPB) and Gram-negative (GNB) bacteria and high stability with beta-lactamases. Small Doxef**.** Levels inhibit most of the respiratory pathogens. (Bergogne-Berezin E1991)The drug is very active in vitro against (the Moraxella spp., the Hemophilusspp,.and the Enterobacteriaceae) ., Like β-lactamase producers and other strains which are resistant with various all oral agents. It exerts GPB activity, especially streptococci. It dose n't work against enterococci. It is High tolerance and The first one (CS)to be produced in third generation (Sarmah AKet al. 2006)It is used orally to treat infections of the respiratory tract that are mild to severe, uncomplicated and urinary tract infections (Cabello FC.2006)

History

In the past, the ancient Chinese used more than (2,500 antibiotics) for the first time. Chinese also The therapeutic properties of moldy soya have been discovered with that drug was used to treat furuncles, carbuncles and related infections. Alexander Several various historical civilizations, including ancient Greeks and Egyptians;, have also plants and Molds used for the procedure diseases from these species because of the availability of antibiotic supplies. But at the time compounds enhancing antibiotic activity were once unknown (Kourkouta L et al. 2017)

The development of Drugs with antimicrobial activity started in the late 1890s, the first antibiotic pyocyanase was discovered by two German researchers, Rudolph Emmerich and Oscar Löw., extracted from Pseudomonas aeruginosa microbe production, The effectiveness and protection of the patient population used against cholera and typhoid is uncertain.

Paul Ehrlich in 1909 added Salvarsan Arsenic-based Drug,That worked against the Treponema pallidum bacterium which is responsible for syphilis disease. This discovery provided the basis for the further development of antimicrobials .The landmark in Antimicrobial Drug Discovery, however, It was once Alexander Flemming's discovery of penicillin in (1928) and Used in physiotherapy to this day. (Georgopapadakou NHet al.1993)

in (1945) An antibiotic-producing species of (CS) used to be isolated from a sewage outfall in Sardinia, Upon introduction of penicillin into the medication. This organism used to be found in Oxford four years later Multiple antibiotics, including penicillin with a different penicillin N, side-chain, were developed. After a chemical discovery in 1953 this penicillin was once considered to be, When a second drug was found to infect this CS, penicillin , which contains a ~lactam ring but is resistant to hydrolysis by (penicillinase) (~lactamase). At the time, a severe problem in hospitals had been caused by (penicillinase)-producing Staphylococci. CEPHALOSPORIN CS (7-ACA) nucleus isolation has allowed pharmaceutical companies to manufacture several hundreds of CS, some of which have been successful in treating severe infections across a variety of GP and GNbacteria's Including the more recent penicillins and CSs have greatly and have a very low toxicity increased The Chemotherapy Spectrum (Barry PM, et al. 2009)Additional families of clinically useful components like β~lactam reactive ring have been published in new responsive screening techniques. You may change the CS nucleus to get different properties. The CSs are usually classified by their antimicrobial properties into "generations."The 1st CSs were distinct CSs of the 1st generation, while later more extended spectrum CSs were known as second-generation CSs (cephalosporin's CSs).Increasing more recent generation Has much higher Gram-Antimicrobial properties than the previous generation with reduced Gram-Species Behavior in most cases. However, (cephalosporinsCSs) of the fourth generation also have very broad-spectrum behavior. CSsare made of five generations. However, various CSs are also chemically identical in the same generation and have different range of action Cefpod. is Is An oral antibiotic, 3rd-generation CS .This is active against most GNspecies, and GP species. Cefpod. free acid is a wide variety of antibiotics targeting a broad range of GP and GN bacteria, especially those causing otitis media and pharyngitis.(Nightingale CH, et al.1975)as shown in the figure (1) Cefpod. proxetil is an orally absorbed cefpod.prodrug, as shown in figure (2) ,A wide variety of, semi-synthetic CS ,It is useful in infections caused by penicillin-and CS resistant bacteria. However, resistance to cefpod. was documented through the development of beta-lactamase .Clavulanic acid is an inhibitor of betalactamase that boosts penicillin and CS activity against several resistant bacterial strains .(Doern GV et al.1980)Clavulanic acid is an important, irreversible inhibitor of Richmond types II, III, IV, and V8 beta-lactamases. Potassium clavulanate is a beta-lactamase inhibitor coupled with cefpod .proxetyl to overcome the bacterial resistance mediated by betalactamase. A fixed dose combination of (potassium clavulanate and cefpod. Proxetil) is available and is marketed as shown in the figure (3)

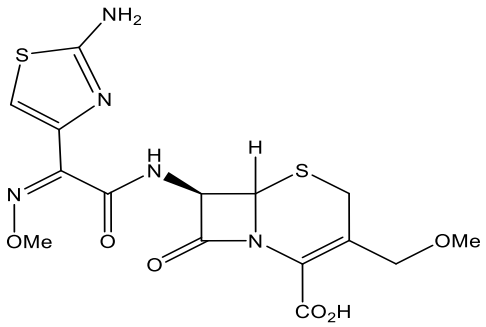


Figure -1:-The chemical composition of Cefpod. free acid

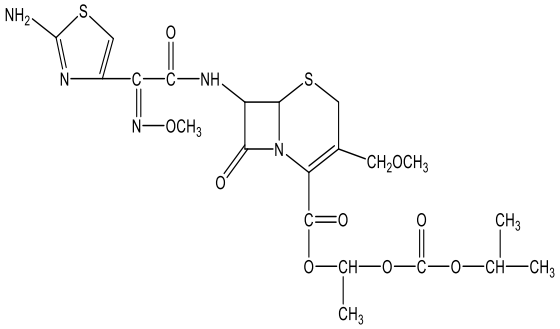


Figure -2 :- The chemical composition of Cefpod.proxetil

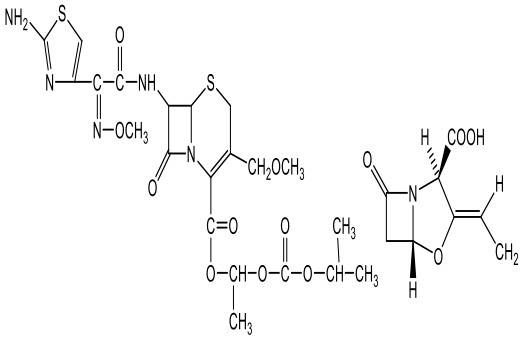
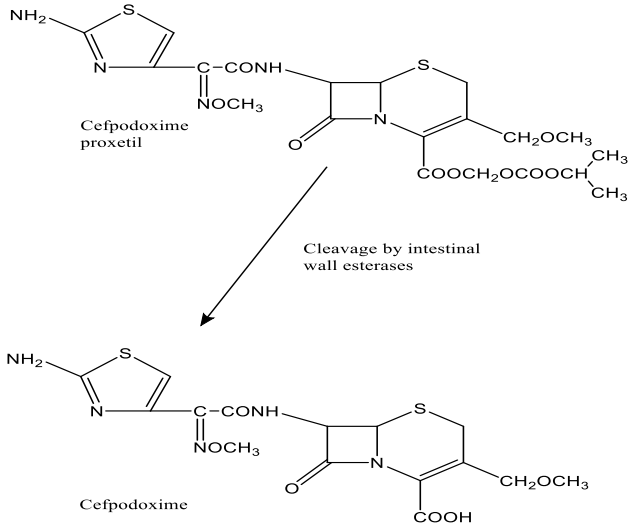


Figure -3:- The chemical composition ofCefpod. proxetil + clavulanate potassium

Physical characteristics of Cefpod. proxetil: Dust White to Light Brownish-White, Smell less or with a mild odour. It is highly soluble in water; Is soluble naturally in dehydrated alcohol for example (methyl alcohol and acetonitrile) ; is somewhat soluble in ether .It could be stored at temperatures no overtaking (25 ° C)in airtight containers. Cefpod. proxetil is a drug favourite. In the gut wall, it is enzymatically bound to2-propanol, carbon dioxide, acetaldehyde, and cefpod. (Rodríguez JC, et al.2003)

Chemical aspects ofCefpod. proxetil: Cefpod. Proxetil is orally absorbed the prodrug of cefpod., an advanced, semi-preparation of CS[20]. The nomenclature is (RS)-1-(isopropoxycarbonyloxy)-ethyl (+)-(6R,7R)-7-[2-(2-amino-4-thiazolyl)-2-{(Z)-methoxy-imino}acetamido]-3-methoxymethyl-8-oxo-5-thia-1azabicyclo[4.2.0] oct-2-ene-2-carboxylate.(Rodríguez JC, et al.2003;Biçer E et al.2013)The empirical formula for it is C21H27N5O9S2 [20]. It is in vivo cleavage shown in the scheme (1)



Scheme (1):- the scheme shows the intestinal cleavage of cefpod. Proxetil prodrug

Mechanism action of Cefpod. Drug

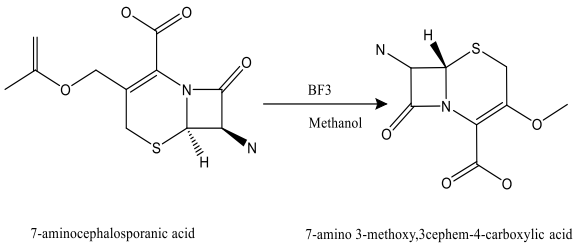
Cefpod. is a semi preparation , CS of the 3rd generation. The drug is safe to use as a treatment proxetyl a prodrug cefpod..It is absorbed from the stomach.. It reaches sufficient levels in most body fluids which exceed the minimum inhibitory concentration (MIC). It is excreted unchanged, by way of the kidneys. Dose needs to be modified in impaired renal function, too. Like the rest of the CSs it is a bactericidal agent. The drug works after desterification through the intestinal esterases by Inhibiting Bacterial Cell Wall Synthesis. The active molecule has Mwt. of (557.6 g/mole) , That makes its free passage through Porins by bacterial cell wall. It then passes through the periplasmic space and associates the penicillin-binding proteins (PBP-1 and PBP-3) in the cell membrane. This binding then affects peptidoglycan synthesis in the cell membrane and thus damages the cell.(Malathi S, et al.2009) It inhibits Staphylococcus aureus, as well as being particularly active against

(Enterobacteriaceae andstreptococci) .Cefpod.'s antibacterial effect is focused on Inhibition of cell wall synthesis, and the drug is bactericidal against nearly tested strains at a concentration equivalent to or 4 times higher than the respective MIC11respectively .

Synthesis of CefpodoximeProxetil

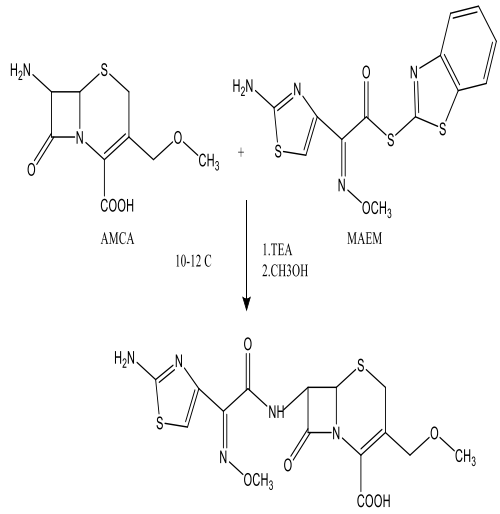
1-cefpod.Proxetil prepared from 7-amino cephalosporanic acid as follows (Rodríguez JC, et al 2003)

A-7-Amino cephalosporanic acid, stirred with methanol in the presence of (10 to 25^{o}C) boron triflouride gas. Preparation of compound (7 amino 3-methoxy,3-cephem 4-carboxylic acid)



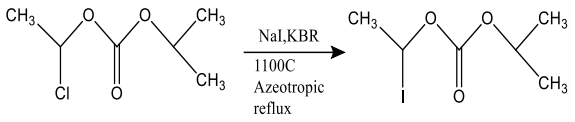
Scheme(2): the scheme show the preparation of compound (7-amino 3-methoxy,3-cephem-4-carboxylic acid)

b-the compound (7-amino 3-methoxy,3-cephem-4-carboxylic acid) with (CH3OH) - stirred and ($(CH_3)_3N$) gradually added at (10-12 c °) to give cefpod. acid



Scheme (3) :- the scheme show the preparation of cefpodoxime acid

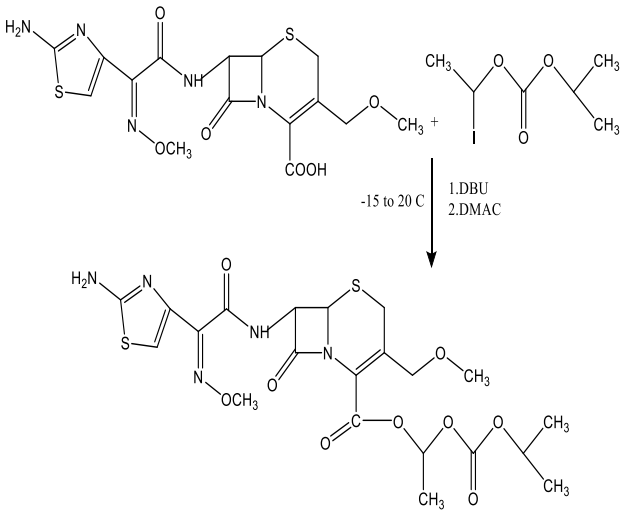
c-Preparation of iodine compound (Side Chain) of Cefpod.Proxitil by conversion of chlorine compound by reaction to NaI, KBr and crown ether at (25^{o}C) . Temp lifted. For azeotropic reflux up to (1100^{o}C)



CHLORO COMPD IODO COMPD

Scheme(4) :- The scheme show the conversion of chloro to iodo compound

D-Cefpod. Acid reacts with iodine compound (side chain) in the presence of (1,8-Diazabicyclo[5.4.0]undec-7-ene) and Dimethylacetamide used as solvent for the preparation of Cefpod. Proxetil



Scheme(5):- the scheme show the preparation of Cefpod. proxetil

2-the compound of acylation of (7-aminocephalosporanic acid (7-ACA))and the HCl(Fujimoto K . et al 1987)In the presence of $CaCl_2$, the compound (3-acetoxymethyl derivative II prepared by acylation of 7-aminocephalosporanic acid (7-ACA)) and HCl. the compound of[(Z)-2-(2-chloroacetamido-4-thiazolyl)-2-(methoxyimino)acetic acid (CATMA)] is treated with aqueous (CH_3OH) to give the corresponding3-methoxymethyl derivative III. The III chloroacetyl group is extracted in aqueous solution by reaction with (NH_2CSNH_2) to give compound IV. Finally, IV esterification with1-iodoethyl isopropyl carbonate (VI) gives the correct VII ester (cefpod. Proxetil)

Tips and uses for Cefpod. Proxetil

Cefpod: Proxetil tablets are used for treating patients with mild to moderate infections caused by the use of susceptible strains of different microorganisms under the conditions set out below(.Brismar B, et al.1993; Borin MT. 1991)

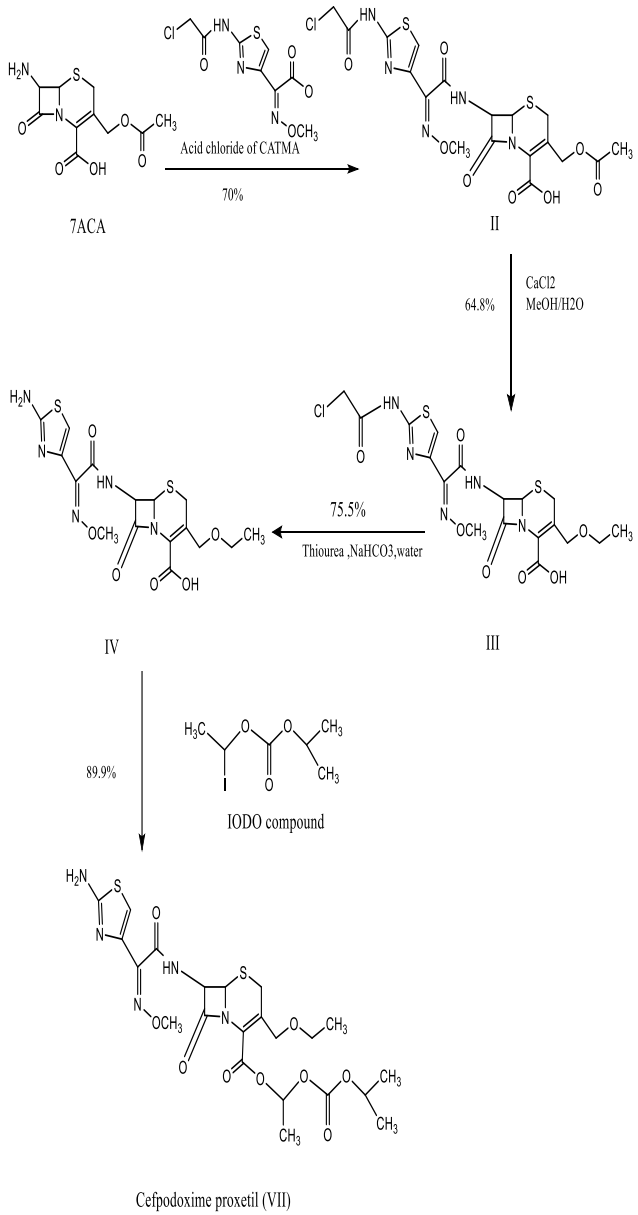
- Tonsillitis and/or. Pharyngitis
- Community-acquired pneumonia Chronic bronchitis exacerbated by acute bacteria
- Acute, uncomplicated gonorrhea of the urethra and cervical
- Acute, uncomplicated anorectal infections Infections of complex skin and skin structure
- Acute maxillary sinusitis Complicated infections of the urinary tract (cystitis)

TABLE 1: The table show the Dosage plan for adults with cefpod.(age 12 years and over)
(Borin MT.1991)

Type of Infection	Total Daily Dosage	Dosage Frequency	Duration
Pharyngitis and/or tonsillitis	(200 mg)	(100 mg every 12 hrs.)	(5 to 10 days)
Acute community acquired Pneumonia	(400 mg)	(200 mg every 12 hrs.)	(14 days)
Acute bacterial exacerbations of chronic bronchitis	(400 mg)	(200 mg)	(every 12 hrs. 10 days)
Uncomplicated gonorrhea (men and women) and rectal gonococcal infections (women)	(200 mg)	(Single dose)	-
Skin and skin structure	(800 mg)	(400 mg every 12 hrs.)	(7 to 14 days)
Acute maxillary sinusitis	(400 mg)	(200 mg every 12 hrs.)	(10 days)
Uncomplicated urinary tract infection	(200 mg)	(100 mg every 12 hrs.)	(7 days)

Cefpod. -Claviulanic acid when caused by susceptible species is indicated in the following infections(Ali MK, et al, 2017)

- Chronic bronchitis acute bacterial exacerbations
- Pneumonia developed by the acute culture
- Upper and lower infections of the respiratory tract
- Skin and soft tissue diseases
- Diseases of the urinary tract
- Pharyngitis and/or tonsillitis
- Gonorrhea general (men and women) and gonococcal rectal (women) infections
- Acute sinusitis maxillary



Scheme(6):- The scheme show the synthesis of cefpod. proxetil in the presence of acid chloride

Conclusion

Cefpod.-Clavulanic acid is a mixture of (two drugs) and is effective against various forms of infection. The portion of clavulanic acid

prevents cefpod. degeneration in the presence of beta-lactamase enzymes, and increases the spectrum of antibiotics.

Preparation of cefpod.-Clavulanic acid prevents resistance to cefpod. Which may increase with the drug's continued use? It has demonstrated efficacy against several (GPB) , (GNB)and generally is well tolerated.

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