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Research Article

Comparative study of antimicrobial activity of two marketed brands (Zinoximore and Cefutil) Kingdom of Saudi Arabia

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ABSTRACT

Oral administration of pharmaceuticals is one of the most popular methods of drug delivery. The drug Cefuroxime is widely used in prescriptions in the Kingdom of Saudi Arabia. This research aimed to study the effect of two marketed brands, Zinoximor and cefutil, and compare them with standard pure drug. This study as post market monitoring of these drugs in community pharmacies. The microbiological sensitivity test was done against both gram positive and gram negative in Escherichia coli, Salmonella typhi, Salmonella para typhi and Staphylococcus aureus. Both drugs were given clear inhibition zone with more effect for Zinoximor, this might be due to high distribution of active ingredient in Zinoximor than Cefutil in formulation process or might be due to distribution of additives.

Key words: Cefuroxime; Microorganisms; Zinoximor, Cefutil; Sensitivity Test Inhibition Zone

INTRODUCTION

Cefuroxime is an antibiotic useful for the treatment of a number of bacterial infections[1], this include middle ear infections, strep throat, pneumonia, traveler's diarrhea, and certain other intestinal infections. It may also be used for a number of sexually transmitted infections including chlamydia and gonorrhea infections. It can be taken by mouth or intravenously with doses once or twice per day, Common side effects include nausea, vomiting, diarrhea and upset stomach. An allergic reaction or a type of diarrhea caused by Clostridium difficult is possible. No harm has been found with use during pregnancy[1]. Its safety during breastfeeding is not confirmed, but it is likely safe[2].Cefuroxime is used to treat a wide variety of bacterial infections. This medication is known as a cephalosporin antibiotic. It works by stopping the growth of bacteria. This antibiotic treats only bacterial infections. It will not work for viral infections (e.g., common cold, flu). Unnecessary use or overuse of any antibiotic can lead to its decreased effectiveness.

Pharmacokinetics of drugs

Following oral administration of cefuroxime axetil, the drug is absorbed from the GI tract as the 1-(acetyloxy)ethyl ester and rapidly hydrolyzed to cefuroxime[3-6]. Cefuroxime axetil has little, if any, microbiologic activity until hydrolyzed in vivo to cefuroxime. Oral suspension is *not* bioequivalent to tablets. In adults receiving film-coated tablets, peak serum concentrations attained approximately 2–3 hours after the dose.[7]

Following oral administration of the oral suspension given with milk or milk products in children, peak serum concentrations attained within 2.7–3.6 hours. Cefuroxime sodium not appreciably absorbed from the GI tract; must be given parentrally. Following IM administration in healthy adults, peak serum concentrations attained within 15–60 minutes. In women, serum cefuroxime concentrations are lower when IM injections are given into the gluteus maximus rather than into the thigh.[7]In adults, bioavailability following oral administration of film-coated tablets averages about 37% when given in the fasting state and 52% when given with or shortly after food. Absorption increased when cefuroxime axetil given with milk or infant formula.[8] The extent (but not rate) of absorption is substantially greater when administered concomitantly with milk compared with applesauce or fasting.[9] Following IM or IV administration, widely distributed into body tissues and fluids including pleural fluid, joint fluid, bile, sputum, bone, and aqueous humor. Therapeutic concentrations may be attained in CSF following IV administration in patients with inflamed meninges. Readily crosses the placenta and is distributed into milk[9].Following oral administration, cefuroxime axetil rapidly hydrolyzed to cefuroxime by nonspecific esterases in the intestinal mucosa and blood.[9] Cefuroxime not metabolized. Cefuroxime axetil is an

oral ester prodrug of the second-generation cephalosporin cefuroxime. Cefuroxime is characterized by a high degree of stability to /J-lactamases and demonstrates favorable in-vitro activity against a wide range of Gram-positive and Gram-negative organisms, including the common pathogens associated with pneumonia[9].

Chemistry:

Cefuroxime axetil is an acetoxyetyl-ester-prodrug of cefuroxime which is effective orally, intravenous preparation (lyophilized 500 mg per10 mL vial).[2]

Fig 1: (1-(acetyloxy) ethyl ester of cefuroxime) is (*RS*)-1-hydroxyethyl (6*R*,7*R*)-7-[2-(2-furyl)glyoxylamido]-3-(hydroxymethyl)-8-oxo-5-thia-1- azabicyclo[4.2.0]-oct-2-ene-2-carboxylate, 72-(*Z*)-(*O*-methyl-oxime), 1-acetate 3-carbamate.

Its molecular formula is $C_{20}H_{22}N_4O_{10}S$, and it has a molecular weight of 510.48. Cefuroxime is an enteral second-generation cephalosporin antibiotic. It was discovered by the Glaxo, now GlaxoSmithKline and first marketed in 1978 as Zinacef. It received approval from the U.S. Food and Drug Administration in October 1983.[1]

Mechanism of Action and Resistance:

The beta lactam antimicrobials exert their antibacterial effects by inhibiting the bacterial beta-lactamase enzyme. This interaction inhibits bacterial multiplication and destroyed bacteria cell wall.[10]

Medical Uses:

Cefuroxime is used to treat many different infections, including acute otitis media, non-streptococcal bacterial pharyngitis, gastrointestinal infections such as traveler's diarrhea, respiratory tract infections such as pneumonia, cellulitis, babesiosis, *Bartonella* infection, chancroid, cholera, donovanosis, leptospirosis, Lyme disease, malaria, *Mycobacterium avium*complex disease, *Neisseria* meningitis, pelvic inflammatory disease, pertussis, scrub typhus, toxoplasmosis, and salmonellosis. It is used to prevent bacterial endocarditis and some sexually transmitted infections. It is also effective against localized dental infections, uncomplicated skin and skin structure infections, urethritis and cervicitis and also genitalulcer disease. Azithromycin is used as a second line treatment for strep throat and for those allergic to penicillin. It has a similar antimicrobial spectrum to erythromycin, but is more effective against certain Gram-negative bacteria, in particular, *Haemophilus influenza* (although it would not be the first choice of treatment in this infection). Cefuroxime resistance has been described and is endemic in many areas. Long-term use in treating *Staphylococcus aureus* infections with azithromycin may increase bacterial resistance to this and other macrolide antibiotics.[10]

Dosage and Administration

Adults:

For respiratory tract infections, otitis media and skin & soft tissue infections: 500 mg twice daily for 5 days or an alternative to this as 750 mg twice on day 1, followed by 500 mg twice daily for next 4 days. For sexually transmitted diseases like genital ulcer, non-gonococcal urethritis and cervicitis due to Chlamydia trachomatis: a single 1.5 gm (1500 mg) dose. For the treatment of urethritis and cervicitis due to Neisseria gonorrhoeae: a single 2 gm (2000 mg) dose. 500 mg twice daily for 7 days in typhoid. In Cholera, a single 1.5 gm (1500 mg) dose. In Shigellosis, 750 mg twice on day 1, followed by 500 mg twice daily for next 4 days.

Children:

Age/body weight Daily dose Duration
From 1month5mg/kg3 days
15-25 kg 100mg 3 days
26-35 kg 200mg 3 days
36-45 kg 400mg 3 days

Post-Marketing Surveillance (PMS)

Post-Marketing Surveillance (PMS*)* is the practice of monitoring the safety of a pharmaceutical drug or medical device after it has been released on the market and is an important part of the science of pharmacovigilance. Since drugs and medical devices are approved on the basis of clinical trials, which involve relatively small numbers of people who have been selected for this purpose - meaning that they normally do not have other medical conditions which may exist in the general population post marketing surveillance can further refine, or confirm or deny, the safety of a drug or device after it is used in the general population by large numbers of people who have a wide variety of medical conditions.[11]

METHODOLOGY

Materials and Culture Media:

Azithromycin powder	used as standard (from India)
Mueller Hinton Agar	(Oxoid Ltd, England)
MacConkey Agar	(Oxoid Ltd, England)
Nutrient Agar	(Oxoid, Ltd) England

Microorganisms:

Isolated (*Salmonella Typhi, Salmonella para Typhi, Staphylococcusaureus, Escherechia coli).*

Microbiological Test:

Microbiological test was carried out for new formula in four isolated laboratory species to inhibit and ensure the effectiveness of the antibiotics. And those species are

Salmonella typhi, Salmonella para, Staph. Aureus and Escherichia coli.[12]

Cefuroxime Sensitivity Test using Disc Diffusion Kirby-Bauer:

For each test and standard 1mg is taken and dissolved in 10 ml distilled water then 1ml was taken from it and dissolved in other10 ml distilled water.[12]

Antibiotic Disc Preparation:

Filter paper was cut into small disks of about 4 mm in diameter then it enclosed in a sealed container and sterilized in oven. Half number of the disks impregnated with cefuroxime test suspension and the others with standard suspension then the disks are dried in oven at $60C^0$ for 20 minutes (serial dilution was made to obtain concentration 10µg/ml as follow: 1mg was dissolve in 10ml and then 1ml was taken and dissolve in another 10 ml).

Dilution factor = $\left(\frac{R \times V}{O}\right)$

Where:

R is required concentration,

V is required volume

O is origin concentration

Inoculums was prepared from each bacterium under test

- *Staphylococcus aureus*
- *E. coli*
- *Salmonella Typhi*
- *Salmonella Para Typhi*

Inoculums preparation is the most important step in any susceptibility test. Inocula are prepared directly by inoculating colonies grown overnight on an agar plate, into broth media. Then the numbers of bacteria tested was standardized using McFarland turbidity standards[15]. McFarland turbidity standards: The McFarland 0.5 standard is used, which contains 99.5 ml of 1% sulfuric acid and 0.5 ml of 1.175% barium chloride, this solution is dispensed into tubes comparable to those used for inoculums preparation. The McFarland 0.5 standard provides turbidity comparable to that of a bacterial suspension containing $1.5*10^8$CFU/ml.[12]

***Inoculation and incubation*:** After preparation of standard inoculums suspension, a sterile cotton swab is dipped into the suspension, pressed to remove excess liquid, and then swabbed evenly across the surface of a Mueller Hinton agar plate (plates of 9mm are used). (Each inoculum suspension was inoculated into three media labeled test (T), standard (S) and control(C)).

- Within 15 minutes of inoculation, the individual cefuroxime disks (one disc per plate) are applied to the agar media with a forceps and gently pressed to ensure contact with the agar.
- The cefuroxime Test disks are applied in the plates labeled (T)
- The cefuroxime acid Standard disks are applied in the plates labeled(S). While other plate's labeled (c) without antibiotic disks were used to control growth.
- Within 15 minutes of disks placement, plates are inverted and placed in a 37°C for 18 hours.
- After incubation the plates were examined, to make certain the test organisms has grown satisfactory, the diameter of each inhibition zone is measured using ruler or calipers.
- Once zone measurements have been made, the millimeter reading for each brand and standard are compared with that specified in the interpretive tables of the NCCLS documents[12].

RESULTS AND DISCUSSION

Table 1- Comparison between the Two Types of cefuroxime Combination with standard on Different Species of Microorganisms

Brand	Diameter (mm)			Surface Area (mm^2)		
	E. Coli	*Staph aureus*	*Salmonella Species*	*E. Coli*	*Staph aureus*	*Salmonella Species*
Cefutil	12	9	11	113.04	63.59	94.99
Zinoximore	14	10	12	153.86	78.5	113.04
Standard	16	11	14	200.96	94.99	153.86

In two types of antibiotic brands tablet (Cefutil and Zoniximore) the zone of inhibition is slightly larger in Zetron than Zomax this might be due to good distribution of active ingredient and both of them is lower than standard (pure powder of cefuroxime).

The disk was used in concentration 10µg according to (Oxoid Ltd, England) to give the require effect. For Accuracy and precession of the result standard *Staphylococcus aureus* according to the national committee for clinical laboratory standards (NCCTS).[12]

The diameter of each inhibition zone was found after measuring, using a ruler and calibers for each brand as shown in Table (1) and Figure 2 and 3. It is clear that arrangement of inhibition zone from microbiological results of zones of inhibition standard >Zinoximore>cefutil. All brands are active against selected bacteria with more *Escherechia coli* and *Salmonella sp*this agreed with Kim *et al.*[14] The response of *Staphylococcus aureus* is less sensitive than *Salmonella typhi, Salmonella pratyphi* and *Escherichia coli* to cefuroxime, that clear in table (1) and figure (2), this due to the effect of second generation of beta lactam group on gram negitive specious like *Salmonella typhi, Salmonella pratyphi* and *Escherichia coli*

rather than gram positive specious like *Staphylococcus aureus*,[13] this result agreed with Susan *et al.*,[15] and Kim *et al.*[14]

Fig 2- Inhibition Zone of *Staphylococcus aureus* with cefutil

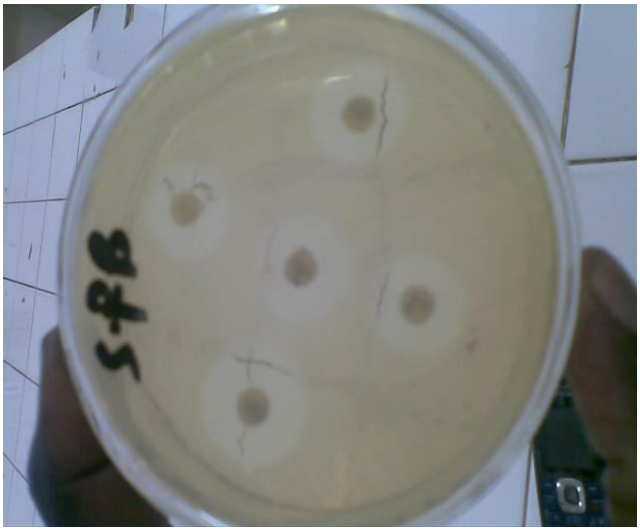

Fig. 3- Inhibition Zone of *Salmonella Typhi* with pure Standard antibiotic.

CONCLUSIONS

- The less sensitivity of *Staphylococcus aureus* comparing to *Salmonellatyphi* may be due to the genetic factor that makes *Staphylococcus aureus* produce beta lactamase which might be responsible for resistance.
- Second generation group (especially cefuroxime) isn't prescribed for gram positive specious microorganisms due the high resistance of these microorganisms to second generation cephalosporin group.
- The monitoring and quality control testing of medicines in pharmacies randomly to ensure the good storage conditions might ensure drug's effectiveness.
- The microbiological sensitivity test can be used as an indicative for variations of drugs activities in different formulae and give good indication for the efficacy of marketed drugs.
- The correlation can be made between microbiological sensitivity tests of different marketed drugs as an indication for its effectiveness in vivo studies.

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