J Toxicol Pharmaceut Sci, 2017; 1(2), 73-77

http://www.jtps.com.pk
Journal of Toxicological & Pharmaceutical Sciences
NEXUS SCIENCE FORUM

ORIGNAL ARTICLE

A cost effective analysis of ceftriaxone brands available in Lahore, Pakistan

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Abstract

Cost effective analysis is an economic analysis which compares the relative costs and outcomes of two or more courses of action in the field of health services. Cost-effectiveness analysis is often used where it may be inappropriate to monetize health effect. Ceftriaxone is a valuable third generation cephalosporin, frequently used to treat myriads of infections caused by Gram positive, Gram negative, aerobic as well as anaerobic bacteria.The present study was designed to evaluate the quality of different brands of ceftriaxone available at different prices. Quality was evaluated by the physicochemical equivalence, amount of endotoxins as well as determination of clinical isolates sensitivity of *Salmonella typhi, Escherichia coli, Klebsiella pneumonia* and *Staphylococcus aureus* by turbid metric method against different brands of ceftriaxone. The physicochemical parameters as well as amount of endotoxins were in the range specified by United States Pharmacopoeia(USP). All organisms showed 100% susceptibility against each brand as shown by CLSI (Clinical Laboratory Standards Institute) susceptibility limit i.e. 8 µg/ml. Hence it is concluded that the physicochemical characteristics and *in-vitro* activity of brands is equal regardless of visible price variations. Thus brands with low price can be used expediently for the treatment of economically compromised patients.

Keywords

Ceftriaxone
Cost effective analysis
Turbidemetric method
CLSI
Physicochemical equivalence

To Cite This Article: Tariq S, Ashraf M, Rasheed MA, Rasheed H and Rehman ZU, 2017. A cost effective analysis of ceftriaxone brands available in Lahore, Pakistan. *J Toxicol Pharmaceut Sci*, **1(2),** 73-77.

Introduction

The miraculous discovery of penicillin by Sir Alexander Fleming revolutionized the world. This incident opened the vista for discovery of a number of new antibiotics which greatly reduced the suffering of humanity.1n 1948, a cephalosporin producing fungus was discovered from a sewage waterfall at Sardinian cost (Anyanwu, 2014) and a new antibacterial activity was obtained from crude filtrates of the *Cephalosporium acremonium* culture. This crude filtrate showed the activity of inhibiting the growth of *Staphylococcus aureus* (Singh & Arrieta, 1999). Further research led to the isolation of parent compound Cephalosporin. Ceftriaxone, a third generation broad spectrum cephalosporin, is successfully used to rule out urinary tract infections (complicated and uncomplicated) caused by, *Escherichia coli, Klebsiella pneumoniae, Staphylococcus aureus, Pseudomonas aeruginosa and Proteus mirabilis* (Masood & Aslam, 2010). It has also been used in the treatment of Lyme disease, typhoid fever, and gonorrhea (Reddy & Subbareddy, 2013). For surgical prophylaxis, the effective use of ceftriaxone is justified. One of the remarkable property of ceftriaxone is long serum half life documenting once or twice dosing daily (Garzone et al., 1983; Richards et al., 1984). In cocaine addicts, the efficacy of ceftriaxone to prevent relapse of cocaine

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addiction has also been investigated.(Knackstedt et al., 2010). Ceftriaxone shows side effects like other cephalosporins (Moskovitz, 1984). In some incidents suppression of aerobic gram negative bacilli and yeast overgrowth have been reported (Samonis et al., 1993). Hypoprothrobinemia and biliary sludging have also been observed in few patients (Xia et al., 1990).

Use of ceftriaxone in Pakistan: In 1982, ceftriaxone was approved and registered by Ministry of Health, Government of Pakistan. Currently 110 brands of ceftriaxone are registered and available in local market (Ali, 2009).

Materials and Methods

Brands collection: Nine brands of ceftriaxone were selected randomly out of which 3 were from lowest, three from intermediate and three were from highest price category. All selected brands were blinded twice before carrying out analysis. All brands were subjected to following test for quality evaluation.

Chemical equivalence: The chemical equivalence of selected brands of ceftriaxone was evaluated by determining percentage of active ingredient and percentage of impurities present in the dosage form.

Assay of active material was carried out by method specified in United States Pharmacopoeia 2011. Instrument used for this purpose was Shimadzu LC-10AVP equipped with analytical column which was stainless steel column (15cm×4.0 mm). The stationary phase was L-1(Octadecyl silane chemically bonded to porous silica or ceramic micro particles, 5 um in diameter). Mobile phase was acetonitrile containing 3.2g of tetraheptyl ammonium bromide: pH 7 buffer: pH 5 buffer: Water (400: 44: 4: 552). Flow rate was 2.0 ml/min and injection volume was 20ul while the detector was UV at 270 nm.

Three dilutions of each selected brand as well as working standard calibrated to USP standard ceftriaxone were 10 µg/ml, 20 µg/ml and 40 µg/ml were used to determine the assay and mean was taken.Column was equilibrated with mobile phase for 45 minutes. Six injections were injected of standard, the mean of which was calculated to determine the standard deviation.

The moisture content from the assay (as is) was eliminated by the following formula

Assay (as is) x 100 /100 – Moisture content

This gives the assay of anhydrous ceftriaxone.

Quantification of impurities: The percentage impurities present in all selected brands was determined and interpreted according to official limits.

Physical equivalence: For the physical equivalence of all selected brands of ceftriaxone following factors were determined

- Physical appearance
- Solubility
- pH
- Moisture content

The results were recorded and interpreted according to the limits specified in USP 2011.

Determination of Amount of Endotoxins Present: Being an injectable preparation the amount of endotoxins must be determined. Amount of endotoxins in each sterilized vial of each selected brand of ceftriaxone was determined by gel clot method (Akl et al., 2011). The results were recorded and interpreted as per official limits.

Determination of MIC against *E.coli, Staphylococcus aureus, Salmonella typhi and Klebsiella pneumoniae:* Minimum inhibitory concentration (MIC) of selected brands of ceftriaxone was determined by microtitration method using 96 well microtiter plate. For *Salmonella typhi, Klebsiella pneumoniae and E.coli*, nutrient broth was used while mannitol broth was used for *Staphylococcus aureus.* Clinical Laboratory standards institute (CLSI) has provided recommendation for Ceftriaxone in its report "Performance standards for antimicrobial disk susceptibility test approved standard M2-A6" in 1997. According to Clinical Laboratory Standards Institute (CLSI) the break points for cephalosporin ceftriaxone is ≤8mg/l. (Kiehlbauch et al., 2000).

Results

The results generated by all quality assessment parameters were correlated with the limits as specified by United States Pharmacopoeia (USP) 2011 and statistically analyzed by one way analysis of variance (ANOVA).

The assay of all the selected brands of ceftriaxone was under the official limits and none of the brands showed assay less than 90%. Graph for the assay of nine brands under study is shown in figure 1.

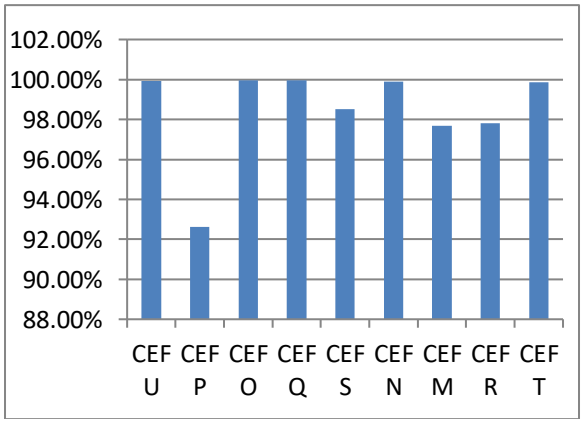

Figure 1: Assay of selected brands of ceftriaxone

Percentage impurity of all the selected brands of ceftriaxone was in official range and none of the brands showed impurity more than 4 %. Percentage impurity of all selected brands of ceftriaxone is shown in figure 2.

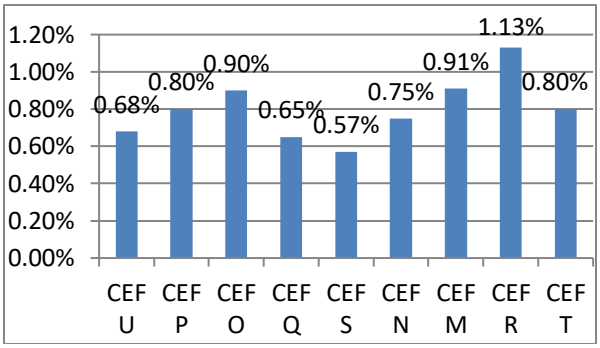

Figure 2: Percentage impurity in all selected brands of ceftriaxone.

The physical parameters of all the selected brands of ceftriaxone showed compliance with official standards. Graphs for pH and moisture content are shown in figure 3 and 4 respectively.The maximum and minimum pH shown by these brands was 7.9 and 6.73 respectively. Similarly, the maximum and minimum moisture content values were 10.034 and 9.147 respectively.

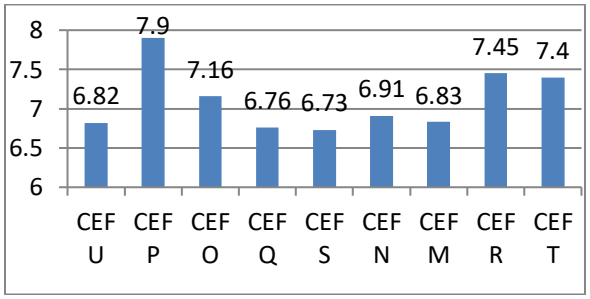

Figure 3: pH of selected brands of ceftriaxone

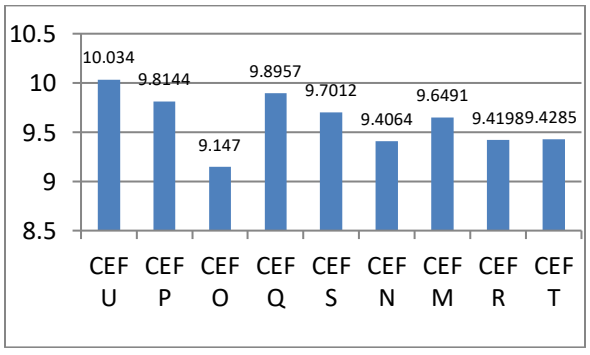

Figure 4: Moisture content of selected brands of ceftriaxone.

All the brands showed 100% susceptibility against *E.coli, Staphylococcus aureus, Salmonella typhi and Klebsiella pneumoniae.* None of the organisms showed resistance against any brand. The graph for MIC of each brands against four organisms is shown in figure 5a while the graph showing the price list of these brands is shown in figure 5b.

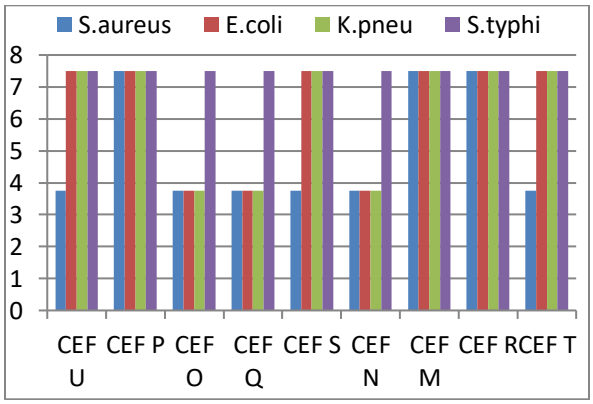

Figure 5a: MIC of selected brands of ceftriaxone against *E.coli, Staphylococcus aureus, Salmonella typhi and Klebsiella pneumonia*

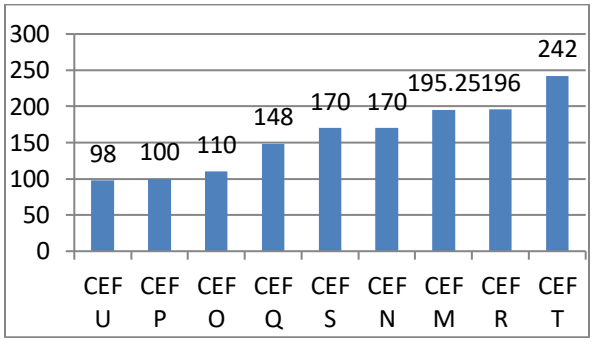

Figure 5b: Price range of selected brands of ceftriaxone in ascending price order

Discussion

The present study was aimed to compare the physicochemical equivalence of different brands of ceftriaxone together with correlation of quality and the price. According to the results it was concluded that irrespective of visible variations in price, there was no variations in quality. Although statistically significant, none of the parameters of any brand showed any deviation from official limits. A similar cost effective analysis was carried out in Karachi and no difference in the quality of brands was observed. In another study, chemical equivalence of 96 brands of ceftriaxone sodium was determined in which none of the brands was found to be substandard (Ali, 2009).Thirty four generic products of ceftriaxone were compared with the

innovator product rocephin, taken as reference standard. All 34 products failed to show compliance with Roche specifications. While 33 products showed presence of thiotriazinone (Jones et al., 2008)

Ceftriaxone is used for the therapy of different infections e.g. community acquired pneumonia, gonorrhea and meningitis. Its long half life and remarkable penetration in tissue and serum protein binding renders it a very important antibiotic (Perry & Schentag, 2001). In a study, the resistance pattern among various pathogens was studied on 5678 bacterial isolates. About 33.8% penicillin resistant strains of *Streptococcus pneumonia*, 25% beta lactamase producing *Haemophilus influenza* isolates and 36.4% amoxicillin resistant *E.coli* isolates. All of these showed fairly good susceptibility to ceftriaxone (Tomlinson et al., 1999)

For correct management of chloramphenicol resistant strains causing meningitis the addition of vancomycin or rifampin to therapy with third-generation cephalosporins is found to be useful (Duke et al., 2003). A study in which 437 gram-negative bacilli clinical isolates were used to know the clinical activity of ceftriaxone. Fifty five adult patients were included in the study. Excellent activity of ceftriaxone was observed overall. The clinical and bacteriological cure rate was 93% (Morgan et al., 1985). Effect of product price and brand information on the subjective quality evaluation of every product was studied. It was found that people tend to purchase a famous brand rather than a brand that has not gained popularity or not marketed appropriately (Dodds & Monroe, 1985).

Certain lapses which are present in drug regulation system of Pakistan require rectification and redefined (Nishtar, 2006).Thirteen clinical isolates isolated from the specimens processed in the Microbiology Laboratory at KMCTH were used. Minimum inhibitory concentration (MIC) of three brands of ceftriaxone was determined and found to be ranged from <0.25 to >256 mg/L (Thapa & Mahat, 2010).

The purpose of agar dilution and broth methods is to determine the lowest concentration of the assayed antimicrobial agent (minimal inhibitory concentration, MIC) which inhibits the visible growth of bacterium being investigated. It is used to evaluate bacterial susceptibilities to drugs and also to investigate the activity of new antimicrobial agents (Pasupuleti et al., 2008). Cost effective analysis is very important in order to establish the priorities for health care program funding (Murphy & Matchar, 1990). As compared to other antibiotics requiring three times daily dosage regimen, single daily dose administration for 12-day treatment protocol would result in saving of about $US392 (Rossini et al., 1998).

Conclusion: From the present study, it was concluded that all the selected brands of ceftriaxone were of standard quality and none of the brands showed any deviation from official limits. The activity of all selected brands was adequate to eradicate *Salmonella typhi, Staphylococcus aureus, E.coli and Klebsiella pneumoniae.* This report can be extremely beneficial to the patients, institutional buyers/donors to pick an effective brand according to their own requirements. If other pharmacological parameters show uniformity, dissimilar brands may be effectively used for reasonably priced treatment of infectious diseases.

Acknowledgements: The study was conducted with the encouragement and support of Department of Pharmacology and Toxicology, University of Veterinary and Animal sciences, Lahore, Pakistan and Pharmagen Private Limited.

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