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SURGICAL SITE INFECTION;

IN-VITRO ANTI-BACTERIAL ACTIVITY OF DIFFERENT BRANDS OF CEFTRIAXONE AGAINST BACTERIA COMMONLY IMPLICATED IN SURGICAL SITE INFECTION AND THEIR COST EFFECTIVENESS

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ABSTRACT… Ceftriaxone is used in wide range of day to day microbial infections in clinical practice[3]. Despite the incumbent drug regulating authority in Pakistan, there is scanty literature comparing the anti-microbial efficacy of different available brands of ceftriaxone. **Objectives**: To know the in-vitro activity of various brands of ceftriaxone against bacteria most commonly isolated from surgical site infection (SSI). A comparison of five days cost of these brands will also be done. **Design:** Experimental study. **Period:** Feb 2013 to Aug 2013 **Setting:** Surgical "C" unit Lady Reading Hospital (LRH) in collaboration with departments of pharmacology Khyber Girls Medical College (KGMC) and microbiology department of Lady Reading Hospital Peshawar. **Material & Methods:** Isolates of five bacteria i.e. Staphylococcus aureus, Proteus mirabilis, Escherischia coli, enterobacter Spp, and Klebsiella pneumoniae, found sensitive to ceftriaxone were grown on 50 slops each and the zone of inhibition was checked for each of the ten brands of ceftriaxone. **Results:** The zones of inhibitions of different brands of ceftriaxone against the above mentioned bacteria were not significantly different. The cost of therapy was significantly different for ten brands. **Conclusions:** Various brands of ceftriaxone of variable cost had no influence on their activity against bacteria involved in SSI.

Key words: Brands of Ceftriaxone, in-vitro antimicrobial activity,SSI,Cost.

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INTRODUCTION

A branded antimicrobial agent must have the same ingredients, formulation, dosage, route of administration and indication as the original drug. Data concerning the standard quality of a product and its stability, and bioequivalence are requested from any pharmaceutical company when applying for the approval of a branded drug[1].

Pakistan is a developing country with high incidence of infectious diseases. The economic consequences of these infections should be considered in evaluating alternative treatment modalities. There are various options for treating these infections. An option that could reduce costs associated with the treatment of infections would have significant financial benefit. On one hand; due to flourishing pharmaceutical industry in Pakistan, clinicians are bombarded with different brands of the same antibiotic to prescribe to their patients while on other hand the health care system in Pakistan makes patients to pay for their medicine. The same product from different companies has a wide price range. All companies claim equally good efficacy compared with research product, but there is lack of evidence in this regard[2].

Ceftriaxone is used in wide range of day to day microbial infections in clinical practice[3]. Despite the incumbent drug regulating authority in Pakistan, there is scanty literature comparing the anti-microbial efficacy of different available brands of ceftriaxone. With background of this knowledge, we planned to conduct an experimental study comparing the in-vitro anti-microbial efficacy and cost of different brands of 'ceftriaxone'.

MATERIAL AND METHODS

This study was conducted to compare in-vitro anti-microbial activity of ten different brands of ceftriaxone available in the local market and hospital. The cost was calculated for five days on average in acutely ill surgical patients, who had undergone, otherwise clean or clean contaminated surgical procedures.

Ten different brands of ceftriaxone available in local market and hospital were used for the purpose. They were coded as C1, 2, 3……10. The codes were secured under key and lock. Only one of the authors knew the exact trade names of ceftriaxone.

Hypothesis

The cost cannot be used as predictor of anti-microbial activity of a branded ceftriaxone.

Technique

Different commercially available brands of ceftriaxone used were coded as C-1, C-2, C-3,… C10. Three hundred slopes of Muller Hinton Agar were prepared by the microbiologist on which five different bacteria were cultured.30 μg Ceftriaxone of each brand was prepared by serial dilution of the available 1gm vials and then instilled with the help of micropipette on filter paper in the culture medium.

Sixty slopes of each of five different microorganisms were grown on Muller Hinton Agar medium according to the standard protocol. The five microorganisms included were:

1. Staphylococcus aureus
2. Proteus mirabilis
3. Escherischia coli
4. Enterobacter spp
5. Klebsiella pneumoniae

Two- three colonies from overnight culture were emulsified in 5ml normal saline in a test tube. Turbidity was matched with 0.5m MC Farland standard. A sterilised swab was then immersed in the tube and then squeezed around the walls to express excess of fluid. A 150mm Muller Hinton agar was then spread with the swab, rotating it at 60 degrees three times to get a uniform bacterial lawn. A solution of concerned ceftriaxone equivelant to 30 ug was instilled on filter paper and then placed in the centre of the plate and incubated at 35+ 2° C at ambient air for 16-18 hours.

After incubation period, zone of growth inhibition appeared around the filter paper. The zones of inhibition including the diameter of the disks were measured, using sliding calipers or a ruler held at the back of the inverted Mueller Hinton plate. Zones were measured to the nearest whole millimeter. The size of the zone of inhibition was interpreted by referring to the interpretive criteria for susceptibility and resistance pattern in accordance with the CLSI break point zone 2012. Based on these criteria, the zone of inhibition was taken as:-

1. Sensitive (23mm or more)
2. Intermediate (20 – 22 mm)
3. Resistant. (19 mm or less)

The cost of different brands for five days was also calculated.

Data Collection procedure

The results were collected as a hard copy and data was analyzed and expressed in the form of tables and charts using SPSS version 20.0. P value less than 0.05 was considered significant.

RESULTS

During the present study, the isolates of various micro-organisms that were sensitive to Ceftriaxone by disc diffusion method were obtained from microbiology Laboratary Lady Reading Hospital, Peshawar.

The zone of inhibition of bacterial isolates namely; Proteus mirabilis, Klebsiella pneumoniae, Enterobacter Spp, Staph aureus and E-coli were evaluated against different brands of Ceftriaxone coded as C1 C2 C3 ----------C10 and comparison was made. A combined average zone of inhibition of different brands of Ceftriaxone is shown in table 1. These values show insignificant difference.

Five days cost of the drug used in this study is shown in table 2, 3. It shows a gross difference in prices of various brands and so is the total cost of average five days therapy. Some of these brands are less expensive and therefore; five days cost is much less than others. Which is very significant .i.e. Mean cost is Rs 2820.0 +1035.8 (P value =0.0001).

Zone of inhibition (mm) – Averages					
	Proteus Mirabilis	Klebsiella Pneumoniae	Enterobacter spp	staphylococcus aureus	E. coli
C1	22.5	21	26	22	22
C2	21	21	25	24	21
C3	22	21	24	25	21
C4	21	23	23	25	21
C5	21	21	23	25	21
C6	21	22	24	26	22
C7	21	21	25	24	21
C8	21	21	24	23	21
C9	21	21	24	25	22
C10	21	21	23	23	21
Mean + SD	21.25 + 0.540	21.30 + 0.674	24.0 + 0.994	24.2 + 1.22	21.3 + 0.48

Table–I.

FIVE DAYS COST OF VARIOUS BRANDS OF CEFTRIAXONE			
S.NO	CODE	COST PER VIAL RS.	COST FIVE DAYS THERAPY
1	C1	220	2200
2	C2	230	2300
3	C3	200	2000
4	C4	320	3200
5	C5	480	4800
6	C6	450	4500
7	C7	260	2600
8	C8	200	2000
9	C9	260	2600
10	C10	200	2000

Table-II.

	N	Mean	Std. Deviation	Std. Error Mean	P Value
Cost	10	2820.0	1035.80	327.54	.0001

Table-III.

DISCUSSION

Bacterial infection has been a longstanding enemy of mankind. The history of development of antibiotics dates back to September 1928, when Alexander Fleming discovered Penicillin[5]. This was a landmark in history after which new antibiotics have been emerging one after the other in an ongoing human race against infection. Ceftriaxone is one such popular drug from the group. It is an extended-spectrum, long acting cephalosporin that soon after its introduction for parenteral use gained wide acceptance as a treatment of choice against many bacteria. Since then, many brands have been marketed and it is being used as a 'workhorse antibiotic[6,7].

Substandard drugs while fail to serve the primary reason for their use i.e. control infection; are more dangerous because of the collateral damage that they cause i.e. production of counterfeit drugs that results in ever increasing resistance to the drug. Because of the escalating problem of drug-resistant pathogens and the limited armamentarium with which to treat them, it is important that we make sure that the drugs while being of different prices are equally effective in their efficacy and strength against the desired bacteria[14].

The subject is being globally addressed to as a self-explanatory term of pharmacoeconomics. Even developed countries like USA are in a constant strife to bring the cost of their drugs down[8]. USA being a free market, manufacturers of pharmaceutical drugs have the freedom to set their own prices for the goods they produce and need not have any particular rationale for their pricing decisions[9]. The issue becomes more crucial in countries like Pakistan, where the major financial burden of the treatment is borne by the patient himself and most of them have very limited resources. Therefore in our country the motive of more brands of drugs is its availability at lower prices. This is being done by introducing new brands of already known drugs at lower costs. For this reason more demand for low priced drugs is in the market both by prescriber and patients.

This phenomenon of patenting of new forms of already known molecules is known as ever greening. In 2005 the Supreme Court of India deemed it unlawful to register a brand of a drug; unless the patent applicant shows significant enhancement in efficacy for its product[10]. However in our country we see 'ever greening' being done for almost every commonly prescribed drug. In a way it is justified to be promoting this phenomenon because at the end of the day we do not want our patients to be left untreated for the mere reason that they could not afford the high cost of generic drugs. In Pakistan currently 154 brands of ceftriaxone are available in the market for variable prices[11]. This figure is higher in India where 1209 Ceftriaxone brands have been registered by 210 companies. If we compare this with the western developed world we would see the limited number of brands that they use[12]. It is very crucial that while we accept a low cost drug, we must ensure that it is as effective as the generic competitor. Nowadays the requirements for authorization to commercialize a branded antimicrobial agent are focused on demonstration of bioequivalence to the original molecule, with a range variability of + 20%.Thus while brands can represent an opportunity for physicians, patients and healthcare systems the regulatory procedures do not seem exhaustive. It is probably necessary to define an ad hoc technical standard of quality before their commercialization by performing adequate clinical trials regarding efficacy and safety of the "equivalent molecule"[13].

Pakistan's pharmaceutical industry currently ranks sixth in the world with export potential of PRs. 300 billion and a growth rate of 17 percent[15]. Moreover while we are deficient in the therapeutic efficacy studies.Post-marketing surveillance is crucial and should be regularly conducted by the health regulatory authorities so that our health system is tailored to our needs and constraints. It is critical that all health care decisions maker should have as much education in Pharamaco-economics as possible[16]. Costs can be brought down by cutting down on the incentives being offered to the health care providers rather than compromising on the quality of drug[7]. We only analyzed in vitro activity of various brands against the bacteria that were already known to be sensitive to ceftriaxone using the CLSI break point zones[4]. The zone of inhibition in our study is comparable with the findings of Masood H et al[3].

In our study as shown in table we found that all the brands were reasonably effective in-vitro against five bacteria commonly cultured from SSI. These results are similar to those of a study published in a South African journal that demonstrated an excellent level of concordance, between a branded ceftriaxone formulation and a reference pharmaceutical-grade powder. They also used MIC as a measure of microbiological activity according to the same guidelines. In a country with limited resources it is important that we encourage the development of drugs of low cost that are more suitable to our population. Considering the controversy and reports of inferior quality of some brands of antimicrobial agents, we believe that comparative MIC determination serves as a basis for their initial evaluation[6]. Limitation of our study is that we did not do MIC values of various brands. We do intend to proceed further in this regard and conduct more studies based on MIC values. However on the basis of our initial results, we can say that a drug cannot be accepted or condemned on the basis of the

brand it is associated with.

The question of resistance of certain bacteria to ceftriaxone was not taken into consideration. The isolates we studied were all sensitive to ceftriaxone in vitro by disk diffusion method. We therefore concluded that; the marked difference of prices between the products of local, national and international pharmaceutical companies cannot be used to predict the in-vitro efficacy of various brands of ceftriaxone.

RECOMMENDATION

We cannot deny the fact that the standard international companies generously invest in research, whereas the local/national companies focused only on drug production as per already existing standards which is justified in a way for a country where people live below poverty line and the prices of medicines plays pivotal role in health care. It is therefore proposed that:

Regular monitoring and analysis should be carried out at different levels of drugs marketing including post purchase assessment of efficacy of a branded ceftriaxone as a guide towards the establishment of a comprehensive monitoring program for general practitioners.

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"Those who don't know history are destined to repeat it."

Edmund Burke

AUTHORSHIP AND CONTRIBUTION DECLARATION

Sr. #	Author-s Full Name	Contribution to the paper	Author=s Signature
1	Dr. Ahmad Faraz	Writting, Introduction & Discussion	
2	Dr. Abdul Hameed	Pharmacological evaluation	
3	Dr. Fazal Bari	Growth of micro organisms	
4	Dr. Irum Sabir Ali	References	
5	Dr. Hamzullah Khan	Manuscript, final editing	
6	Mr. Fazl-e-Rahim	Sensitivity test in lab	
7	Dr. Amjad Naeem	Data collection and wirting & methodology	
8	Prof. Dr. Mumtaz Kha	Theme, abstract writing	
9	Professor Abid Hussain	Supervised the project	