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Pharmaceutical Quality Analysis of Ceftriaxone Sodium Brands Marketed in Southern Nigeria

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Authors' contributions

This work was carried out in collaboration between all authors. Author OO designed the study. Author EO wrote the protocol and author EOA wrote the first draft of the manuscript. Authors EOA and OO managed the literature searches and authors EOA and EO managed the experimental process and interpreted the data generated. All authors read and approved the final manuscript.

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ABSTRACT

One of the paramount controversies between Physicians and Pharmacists is the issue of generic substitution. Prescribers are compelled to choose from such a large range of brands. The objective of this study was to compare the Pharmaceutical quality of innovator brand of injectable Ceftriaxone sodium with its generic brands that are marketed in Southern Nigeria. Seven brands of injectable Ceftriaxone sodium marketed in some pharmacies in Southern Nigeria were analysed. Standard physical and chemical tests for quality control of parenterals approved by the British Pharmacopoeia were performed on the branded sampled. The tested brands complied with the BP specifications for quality of Parenterals. Although one of the generic brands has content weight of Ceftriaxone greater than the upper limit specified (127.906%). The brands of Ceftriaxone sodium tested have been proven to be pharmaceutically and therapeutically equivalent. Though, there are variations among these brands due to the different manufacturing processes and formulation factors.

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Keywords: Ceftriaxone sodium; pharmaceutical quality; quality control; generic substitution; pharmaceutical equivalence.

1. INTRODUCTION

Ceftriaxone sodium, chemically defined as, Disodium (6R,7R)-7-[[(2Z)-(2-aminothiazol-4-yl)(methoxyimino)acetyl]amino]-3-[[(2-methyl-6-oxido-5-oxo-2,5-dihydro-1,2,4-triazin-3-yl)sulphanyl]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate 3.5 hydrate; with the chemical formula, $C_{18}H_{16}N_8Na_2O_7S_3,3^1/_2H_2O$, and a calculated molecular weight of 661.59, is a third generation cephalosporin antibiotic. It has the following structural formula:

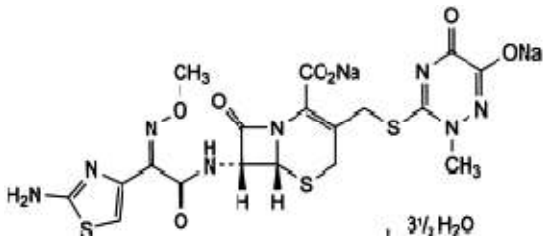

Fig. 1. Ceftriaxone sodium

Antibacterial action of Ceftriaxone sodium is produced through the inhibition of mucopeptide synthesis in the bacterial cell wall and by binding to one or more of the penicillin-binding proteins (PBPs) which in turn inhibits the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus hindering bacterial cell wall biosynthesis. This leads to subsequent cell death by lysis due to on-going activity of cell wall autolytic enzymes continues while cell-wall assembly is arrested [1,2]. Ceftriaxone sodium is well absorbed intramuscularly and possesses a complete bioavailability after intramuscular and intravenous administration. Urinary excretion is the major elimination pathway for Ceftriaxone sodium. As such, 33-67% of dose is excreted in urine as unchanged drug and the remaining fraction is eliminated in faeces through bile. Biliary elimination is significant for Ceftriaxone sodium [3,4].

A generic medicine is defined as an exact simulation of an established drug, not protected by a patent and promoted with the chemical name of the active ingredient. Generic drug formulation contains the same active pharmaceutical ingredient(s) in the same quantity as the reference listed drug (RLD) or innovator brand. There are legitimate concerns about the efficacy of generic formulations, and data show that cost-savings to the patient or the health care system may not be significant as expected [5].

The interchangeability of innovator brands with generic brands is dependent on the evidence of pharmaceutical equivalence, therapeutic equivalence and bioequivalence between the innovator and generic brands. Drug products are considered to be pharmaceutical equivalents if they contain the same active ingredients and are identical in strength or concentration, dosage form, and route of administration. Two pharmaceutically equivalent drug products are considered to be bioequivalent when the rates and extents of bioavailability of the active ingredient in the two products are not significantly different under suitable test conditions. Therapeutic equivalence in parenteral dosage forms is evaluated from pharmaceutical equivalence between the innovator brand and the generic brand, provided that the delivery of the active pharmaceutical ingredient(s) occurs directly in the systemic circulation (100% bioavailability) [6].

Generic brands must meet the official specifications for quality provided by different pharmacopoeias for a standard drug. Standards of a quality drug formulation including; safety, efficacy, purity, stability and potency; must be fully met by the generic formulation. Quality control requirements for parenteral dosage forms include; Visual inspection, clarity, color, and labelling; Uniformity of weight; Uniformity of content; Bacterial endotoxins-pyrogens; Sterility; and Particulate contamination: Visible and sub-visible particles [7].

Several investigations on the pharmaceutical quality of generic drug products have been carried out [8-11]. Previous studies mostly compared innovator brands and generic brands in terms of their physicochemical activities. The studies on Ceftriaxone sodium [12-14]. compared the quality of generic brands with Rocephin®. The limitations of the above studies include non-inclusion brands which are available in Nigeria and also no microbiological assay. Furthermore, as a result of usual controversies between Physicians and Pharmacists on the issue of generic substitution, this study provides evidence upon which such choices can be made in a more accurate, scientific and professional manner.

To the best of our knowledge, no such analysis for Ceftriaxone sodium generics available in Nigerian drug markets has been reported.

Therefore, the aim of this study was to compare the Pharmaceutical quality of innovator brand of Ceftriaxone sodium for injection with its generic brands that are marketed in Southern Nigeria in order to provide evidence of pharmaceutical and therapeutic equivalence that ensures interchangeability and generic substitution.

2. MATERIALS AND METHODS

2.1 Chemicals

The innovator brand (Rocephin®) and generic brands (Protedex® 'PC', Biocef® 'BC', Kincef® 'KC', Ebecef® 'EC', ZMC® 'ZC' and Xapo® 'XC') of Ceftriaxone sodium injection (1000mg) marketed in Nigeria were purchased from approved wholesale pharmacies in Southern Nigeria. These samples were stored at temperature <25℃ in a cool place, prevented from having direct access to light and thereafter tested within their expiration dates. The sampled generics represent the largest proportion of Ceftriaxone sodium for injection 1000 mg easily accessible in Nigeria. Table 1 provides the description of the Ceftriaxone brands sampled. Others include; Phosphate buffer solution pH 7.4, distilled water, ethanol, sterile water for injection, Sabouraund dextrose agar, Mueller-Hinton agar, plate count agar, GenScript ToxinSensor™ Chromogenic LAL Endotoxin Assay Kits (16 rxns) Cat. No. L00350C Lot No. C50181409 which contains Limulus Amoebocyte Lysate (LAL), LAL reagent water, *E. Coli* endotoxin standard, chromogenic substrate, buffer S for color-stabilizer #1, color-stabilizer #1, color-stabilizer #2 and color-stabilizer #3.

2.2 Physical Assessment and Physico-chemical Analysis

The primary and secondary packages of the brand samples were examined very carefully to check for required information such as manufacturers address, manufacturing dates, batch numbers, expiry date, and amount of active ingredients & National Agency for Food and Drug Administration and Control (NAFDAC) Registration number.

Melting point determination and pH value (acidity or alkalinity); were carried out on all brands sampled.

2.3 pH Determination

The pH value was determined using pH meter (PHS – 25 pH Meter, China). British Pharmacopoeia specification for pH of a solution containing the equivalent of 12.0% $^{w}/_{v}$ of Ceftriaxone sodium is 6.0 to 8.0.

2.4 Melting Point Determination

These tests were carried out on all brands sampled and the test were performed using procedures specified by the British Pharmacopoeia 2012, except where otherwise stated. The melting points of the brands were determined using melting point apparatus (Electrothermal, USA).

2.5 Pharmaceutical Quality Analysis

Color of vial content and reconstituted solution, clarity of solution, weight uniformity, content uniformity, sterility, bacterial endotoxin test, particulate matter determination: Visible matter; were carried out on all brand samples. These tests were performed according to British Pharmacopoeia 2012, except where otherwise stated.

2.6 Colour of Vial Content and of Reconstituted Solution

Color of vial content was assessed visually by examining a small quantity of powder placed on a flat white and then black background/surface. The color of the reconstituted solution was assessed by examining a 12% w/v aqueous solution in a clean colourless test tube placed against a white background. The British Pharmacopoeia 2012 specification for color of ceftriaxone sodium for injection is almost white or yellowish powder and the reconstituted solution should not be more coloured than reference solution.

2.7 Clarity of Solution

Samples were reconstituted as directed by the leaflet inserted in the drug package. Clarity of reconstituted solutions was observed against a visual inspection board with a black and white background under sufficient illumination. The presence of black particles was seen using white background whereas any white particles and fibres present were observed against black background. Rocephin® specification is

Table 1. Descriptions of the ceftriaxone sodium 1000 mg brands tested

Product	Manufacturer	Marketing company	Batch number	NAFDAC number	Manufacture date	Expiry date
ROCEPHIN®	Hoffmann-La Roche, Switzerland.	Swiss pharma, Nigeria.	B0112B03 F0527	04-7302	10/2013	10/2016
PROTEDEX®	GlaxoSmithKline, Italy.	GlaxoSmithKline, Nigeria.	T043	B4-0365	01/2014	01/2016
BIOCEF®	Shenzhen Pharmaceutical, China.	Biofem Pharmaceuticals Nigeria	20130802	A4-1459	08/2013	02/2016
KINCEF®	Yangzhou Pharmaceutical, China.	Kingzy Pharmaceuticals Nigeria	140572	A4-7429	05/2014	05/2017
EBECEF®	Swiss Parenterals PVT, India.	Elbe Pharma., Nigeria	XB-14007	04-8977	01/2014	12/2016
ZMC®	Shandong Pharmaceutical, China.	Demytex Pharma., Nigeria	140131	A4-8141	01/2014	01/2017
XAPO®	Swiss Parenterals, India.	Justeen Pharmaceuticals, Nigeria.	XB-13125	04-7267	09/2013	08/2016

(n = 10 per brand)

maximally six visible particles per container and maximum 20 per 10 containers, and maximum 600 sub-visible particles ≥25 mm per container. The British Pharmacopoeia specifies that a solution containing the equivalent of 1.20% w/v of ceftriaxone is clear.

2.8 Labelling Inspection

The label on the vials and the packs were inspected thoroughly and the written instructions were noted and compared with the British Pharmacopoeia specification for labelling of parenteral products and Ceftriaxone for injection.

2.9 Uniformity of Weight

The labels on ten containers of each brand were scraped off and their closures were also removed. Without labels and closures/caps these ten vials were weighed individually, then emptied, rinsed with water and ethanol, dried at 105^0C for 1 hour, cooled, and then weighed again. The weight of the vials with drug, and the weight of the empty vials were recorded. The weight difference was recorded as the weight of vial content. The percentage deviation of each vial-content from the average vial content was calculated and the results compared to the standards in the British Pharmacopoeia [7].

2.10 Uniformity of Content

The content of active substance of each brand sample was determined using ultraviolet (UV) spectrophotometry according to the method described by Bhaskar-Reddy and Subbareddy, 2013.

2.11 Sterility

The vial content was dissolved in the sterile water for injection (10 ml) provided with the preparation. The antimicrobial activity of the drug solution was neutralized by dilution in a sufficient quantity of sterile culture medium. As such, concentrated culture media (i.e. double strength) were used. Two culture media; double strength plate count agar and double strength sabouraund agar, were used for the test.

A 0.1 ml of drug solution was transferred into molten double strength plate count agar and another 0.1 ml was also transferred into molten double strength sabouraund dextrose agar. These were then transferred into sterile petri dishes, allowed to solidify, inverted and incubated; plate count agar at 35-37℃ and; sabouraund dextrose agar at 25℃. These were repeated for all brands.

Microbial growth on the incubated culture media was checked after 3, 7, and 14 days of

incubation. Three vials per brand sample were tested.

2.12 Bacterial Endotoxins-pyrogens Test

Bacterial endotoxins were determined with GenScript ToxinSensor™ using the quantitative endpoint chromogenic method for the measurement of the endotoxin concentration. Three vials per product were tested. British Pharmacopoeia specification is an endotoxin limit concentration of 0.80 IU per mL.

2.13 Microbiological Assay

Antibiotic susceptibility assay was carried out using Muellar-Hinton agar; direct colony suspension, equivalent to a 0.5 McFarland standard for the clinical isolates of *Staphylococcus aureus;* and incubation conditions; 35± 2℃ for 18 hours. The diameter of the zones of growth inhibition produced by the different brands was measured (CLSI, 2013).

2.14 Statistical Analysis

Data was entered in statistical software SPSS 14.0. ANOVA was performed to compare results of assay, Uniformity of weight, Bacterial endotoxin test, and Agar diffusion bioassay of different brands of Ceftriaxone sodium at a 0.05 level of significance.

3. RESULTS AND DISCUSSION

3.1 Physical Assessment: Physico-chemical Analysis

The physicochemical characters analyzed include pH, melting point, color of vial content and color of reconstituted solution and clarity of solution. The results obtained from these tests are expressed in Table 2.

pH is a critical variable and an important factor in the formulation of pharmaceutical products. It serves as a measure of the acidity/alkalinity of substances. The pH of a pharmaceutical product has a great influence on its solubility, stability, palatability and optimal microbial effectiveness (MIC_{max}) i.e. for antimicrobial agents. The product pH may reflect the intrinsic pH of the active pharmaceutical ingredient. All samples tested satisfied the British Pharmacopoeia [7] specification for the pH of ceftriaxone sodium for injection; 6.0 to 8.0.

Melting point is a physical property of drug substances and other chemicals. The melting point or range of a drug can be used as an indicator of purity of chemical substances. A pure substance is characterized by a very sharp melting point. Altered values of melting point temperature may indicate an admixed, impure substance or degradation product(s). Ceftriaxone sodium for injection, a formulation containing the active drug – Ceftriaxone and other excipients in the formulation, gave a melting point range that is lower than the melting point of pure Ceftriaxone. The degree to which the melting point is lowered is dependent on the excipients used in formulation. Hence, the generics of ceftriaxone sodium have different melting point ranges [15].

3.2 Pharmaceutical Quality Analysis

Parenteral drug products, especially those administered as liquid solutions should be free of particulate matter. For particulate matter determination: Sub-visible and visible particles, as a result of non-availability of the equipment for sub-visible matter determination, this study only looked at the visible matter content in the reconstituted solutions. On visual inspection of the reconstituted solutions of each brand sample, no visible particle was seen in samples KC, EC, ZC and RC. Though, visible particles were present in the reconstituted solutions of BC, PC & XC but their numbers were within the acceptable range (< 6 particles per vial or < 20 particles per 10 vials). The scope of this study does not include determination of exact identity of the observed particles. Some investigators suggest the presence of such particles in parenteral products may compromise tissue perfusion and impact the microcirculation, which may be clinically significant for the critically ill patients [16,17].

On inspection of the labels on the vials and the packs of different brands, all generics brands tested met the BP [7] specification for labelling of Ceftriaxone sodium for injection.

The average weight of all brand samples tested where within BP [7] specification for uniformity of weight of single dose preparations. They fall within 92.44-100.03% of the innovator product. This implies that there is an acceptable variation from the innovator brand. Although the intra-batch variation was high in two brands: Protedex® and Kincef®. The implication of this is that both brands may produce variable plasma

concentration in the patient. The variations in the average weights of the different brands tested can be attributed to different formulation and manufacturing factors.

The content uniformity of the samples was assayed in phosphate buffer pH 7.4. Ceftriaxone showed maximum absorption at 320 nm. Linearity was observed in the concentration range 5-40 µg/ml and a calibration curve with correlation coefficient value 0.9961; slope 0.0033 and intercept 0.01 were obtained. The concentration of Ceftriaxone in the samples was obtained through extrapolation from the Beer-Lambert plot. These variations in content uniformity of the samples were attributed to formulation and manufacturing factors.

All the samples of Ceftriaxone sodium tested comply with the BP [7] specification for content uniformity of Ceftriaxone sodium for injection with exception of sample BC where the content was 127.91% against the standard value of 92-108%. The implication of the significant differences observed between other samples and BC may be due to non-adherence of manufacturer of sample BC to good manufacturing practices.

Sterility testing was carried out on the samples and no microbial growth was observed after 3, 7 & 14 days of incubation. The implication is that, neither bacteria nor fungi are present in the brand samples tested. Thus, the generic products tested comply with the BP 2012 specification of Sterility for parenteral products.

The standard specification of bacterial endotoxins for Ceftriaxone preparations is 0.8 IU/ml (BP). With exception of sample BC (0.8078 EU/ml) which technically (since it does not significantly differs from the upper limit) fails this test all other brands and the innovator product pass the test of content of bacteria endotoxin.

The samples of different brands of Ceftriaxone sodium tested produced distinct and clearly defined zones of growth inhibition on *Staphylococcus aureus* inoculated agar. The size of zones of inhibition produced with respect to the amount of drug used for the test indicates that the microorganism is susceptible to the antibacterial activities of the different brands of Ceftriaxone sodium tested. However, differences were observed in the magnitude of growth inhibition. ANOVA was adopted to compare the Zones of Inhibition produced by different brands of Ceftriaxone sodium. Results of ANOVA showed that there was significant influence of brand on the zones of growth inhibition of *Staphylococcus aureus* produced (p-value<0.05). This variation is attributed to formulation and manufacturing factors and thus account for why some of the brands are more efficacious than some other brands. The following order from maximum to minimum zone BC>KC>XC>EC>PC>RC>ZC was observed. The trend of zone of inhibition produced by various brands correlate with their content of ceftriaxone sodium. Therefore, sample BC with highest content produced the highest zone of inhibition. Thus, supporting the assertion of previous workers that there is a linear relationship between zone of microbial growth inhibition and the potency of antibiotics [18,19].

Table 2. Physical description and physicochemical characteristics of innovator and generic ceftriaxone sodium

Product	Physical description			Physicochemical characteristics	
	Color		Appearance	pH	Melting point (℃)
	Dry powder	Reconstituted solution			
Rocephin®	Off-white	Pale yellow	Fine powder	6.70	205-215
Protedex®	Off-white	Pale yellow	Fine powder	7.06	208-210
Biocef®	Off-white	Pale yellow	Fine powder	6.70	180-182
Kincef®	Off-white	Pale yellow	Fine powder	6.87	202-204
Ebecef®	Off-white	Pale yellow	Fine powder	6.66	210-216
ZMC®	Off-white	Pale yellow	Fine powder	6.87	180-185
Xapo®	Off-white	Pale yellow	Fine powder	6.88	220-222

Table 3. Pharmaceutical (chemical and microbiological) quality of innovator and generic brands of ceftriaxone sodium tested

Product	Visible particles	Average weight (mg) ± SEM	% content of ceftriaxone	Sterility	Endotoxin content (EU/mL)	Zones of inhibition (mm) ±SEM
Rocephin®	0	1190.5±5.31	100.00	No growth	0.4951	23.17±0.98
Protedex®	4	1190.8±15.67	105.72	No growth	0.6699	23.67±0.42
Biocef®	4	1178.2±5.98	127.91	No growth	0.8078	28.00±1.51
Kincef®	0	1100.5±10.19	97.87	No growth	0.7569	24.33±0.33
Ebecef®	0	1180.3±6.03	101.17	No growth	0.5861	23.83±0.65
ZMC®	0	1083.0±4.76	100.00	No growth	0.6061	21.33±0.21
Xapo®	2	1168.0±6.19	101.66	No growth	0.5067	24.33±0.21

4. CONCLUSION

The Pharmaceutical quality testing carried out on the innovator and six generics of ceftriaxone sodium for injection using standard quality control tests of Weight Uniformity, Uniformity of Content, Clarity, Sterility and Bacterial endotoxins-pyrogens with the aim of evaluating whether they are pharmaceutically equivalent and/or therapeutically equivalent, has been confirmed. The results obtained from this study match that of BP [7] standards and specifications, indicating that all brands tested can be pharmaceutically and therapeutically interchanged. Quality control tests are important and should be carried as one of the pharmacovigilance programs of drug regulatory agencies and by researchers in both developing and developed countries.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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