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Research Article

Bioequivalence Study of Two Formulations of Cephalexin Powder For Oral Suspension in Healthy Subjects Under Fasting Conditions

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ABSTRACT

Objective: The present study was conducted to the bioavailability of two formulations of cephalexin 250 mg powder for oral suspension administered in fasting condition in healthy subjects are equivalent.

Materials and Method: This study was an open-label, randomized, single-dose, twoperiod, two-sequence, cross-over study under fasting condition which included 20 healthy adult male and female subjects under fasting condition. Blood samples were taken and analyzed for plasma concentration of cephalexin using selective and sensitive HPLC-UV method This study consisted of two periods, each 6 hours interspaced by washout period for 7 days between doses (test and reference). The pharmacokinetic parameters assessed in this study were the maximum plasma concentration (Cmax), the area under plasma concentration-time curve from time zero to the last observed concentration(AUC0-t), the area under plasma concentration-time curve from time zero to infinity (AUC0-inf), the time to achieve the maximum plasma concentration (tmax), and the terminal half-life (t½).

Results: After a single-dose administration of cephalexin 250 mg powder for oral suspension, the mean (SD) value AUC0-t and Cmax of test product were 19622.05 (5020.31) ng.h/mL and 13305.52 (3290.83) ng/mL, respectively; the mean (SD) value AUC0-t and Cmax of reference product were 19124.08 (3388.27) ng.h/mL and 14920.71 (3404.05) ng/mL, respectively. The geometric mean ratios (90% CI) of the test drug/comparator drug for cephalexin were 101.34% (97.48-105.35%) for AUC0-t and 88.78% (80.73-97.64%) for Cmax. There were thirteen adverse events reported during this study.

Conclusion: The present study was concluded that two cephalexin powder for oral suspension formulations were bioequivalent.

Keywords: Bioavailability; Bioequivalence; Cephalexin; Antibiotics; Beta-lactam; Pharmacokinetics

INTRODUCTION

Beta-lactam antibiotics are one of the most commonly prescribed drug classes with numerous clinical indications. From biochemical point of view, these drugs have a common feature, which is the 3-carbon and 1-nitrogen ring (beta-lactam ring). Of the beta-lactam antibiotics that are currently available there are five relevant ring systems, including the penam, penem, carbapenem, cefem and monobactam ring structure [1,2].

The mechanism of action of beta-lactam antibiotics is related to inhibition of bacterial cell wall. Bacteria synthesize a cell wall that is strengthened by cross-linking peptidoglycan units via penicillin-binding proteins (PBP, peptidoglycan transpeptidase). The beta lactam rings bind to the penicillin-binding protein and inhibit its normal activity. The bacteria will be unable to synthesize a cell wall and then died [3-5].

Cephalosporin, initially derived from the fungus Cephalesporium sp., is the major representative of cephems group, has been among the most potent and most widely used anti-invective agents. Traditionally, Cephalosporin are divided into first-generation, second-generation, third-generation, fourth-

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generation and fifth-generation, according to antibacterial activity. First-generation cephalosporin are very active against Gram-positive cocci, except enterococci and methicillin-resistant staphylococci, and moderately active against some Gram-negative rods primarily *Eschericia coli*, *Proteus*, and *Klebsiella*. One of commonly used first-generation oral cephalosporin is cephalexin (Figure 1).

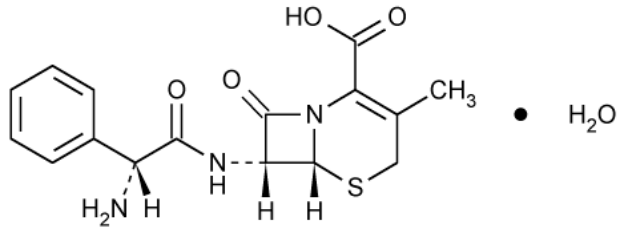


Figure 1: Chemical Structure of Cephalexin monohydrate.

Cephalexin or cefalexin, (6R,7R)-7-[(R)-2-amino-2-phenylacetamido]-3-methyl-9-oxo-5-thia-1-azabicyclo [4.2.0]oct-2-ene-2-carboxylic acid, monohydrate has molecular formula $C_{16}H_{17}N_3O_4S.H_2O$ and molecular weight 365.41, is a semi-synthetic cephalosporin antibiotic for oral administration route. Its appearance is white or almost white crystalline powder which slightly soluble in water; practically insoluble in alcohol, chloroform, & ether and has structural formula as shown in Figure 1 [4-7].

Cephalexin is absorbed from the gut to a variable extent and indicated to be used to treat respiratory tract infections; otitis media; skin and soft tissue infections; bone and joint infections; genito-urinary infections; including acute prostatitis and dental infections. Cephalexin is active against the following organisms in vitro: β-haemolytic streptococci; staphylococci, including coagulase-positive, coagulase-negative and penicillinase-producing strains; *Streptococcus pneumoniae*; *Escherichia coli*; *Proteus mirabilis*; *Klebsiella species*, *Haemophilus influenzae*; *Branhamella catarrhalis* [8-10].

Cephalexin is administered orally as either 250 mg or 500 mg that can be given 1 to 4 times a day usually for seven days. Most of infections will respond to a dosage of 500 mg every 8 hours. For skin and soft tissue infection, streptococcal pharyngitis, and mild, uncomplicated urinary tract infections, the usual dosage is 250 mg every 6 hours or 500 mg every 12 hours [8,9].

Cephalexin is rapidly absorbed after oral administration. Following doses of 250 mg, 500 mg, and 1 g, average peak serum levels of cephalexin are approximately 9, 18, and 32 mg/L, respectively, were obtained at 1 hour. Measurable levels were present 6 hours after administration. Absorption is slightly reduced if the drug is administered with food. Peak blood levels are achieved one hour after administration, and therapeutic levels are maintained for 6-8 hours. No accumulation is seen with dosages above the therapeutic maximum of 4 g/day. Cephalexin is approximately 10% to 15% bound to plasma proteins. Cephalexin is almost completely absorbed from the gastro-intestinal tract, and 75-100% is rapidly excreted in active form in the urine. It was found that over 90% of the drug was excreted unchanged in the urine within 8 hours. The half-life is approximately 60 minutes in patients with normal renal function. Hemodialysis and peritoneal dialysis will remove cephalexin from the blood. The half-life may be increased in neonates due to their renal immaturity, but there is no accumulation when given at up to 50 mg/kg/day [11].

The following side effects have been reported during administration of cephalexin: diarrhoea, nausea, vomiting, indigestion, stomach pains, measles-like rash, itching, urticaria, rash with spread joint paint and or stiffness, swollen lymph glands, fever, cloudy urine, changes in blood counts, damage to liver or kidneys, jaundice, weakness, fainting, abnormally excitable behaviour, agitation, tiredness, headache, confusion, dizziness, hallucinations, candidiasis, a red scaly widespread rash wit bumps under the skin and blisters accompanied by fever. Cephalexin is contraindicated in patients with hypersensitivity to cephalexin or other members of the cephalosporin class of antibacterial drugs [12].

Bioavailability and bioequivalence of drug products have emerged as critical issues in pharmacy and medicine. Bioequivalence testing is considered as a surrogate for clinical evaluation of the therapeutic equivalence of drug products. The therapeutic equivalence of two products are assessed from average Cmax and AUC calculation. Bioequivalence data and quality system are needed for generic product registration [13-15].

MATERIALS AND METHODS

Prior to study can be initiated, study protocol and informed consent was developed according to Declaration of Helsinki; GCP Principle; OECD Principles of GLP; Guideline on the Investigation of Bioequivalence, EMA; ASEAN Guideline for the Conduct of Bioequivalence Study, Lao PDR; and Indonesian Guidelines. The final protocol had been approved by Independent Ethics Committee (IEC) of Medical Faculty, Universitas Indonesia and local regulatory authority, BPOM [16-19].

This bioequivalence study was an open-label, single-dose, randomized, two-period, two-sequence cross-over study under fasting condition interspaced by 7 days washout period between doses, which included 20 healthy subjects. In this study, the product to be investigated were Cefalexin 250 mg powder for oral suspension produced by Imexpharm Corporation (test drug) in compare to Cefalexin 250 mg/5 mL granules for oral suspension, Flynn Pharma Ltd., Ireland (comparator drug). The bioequivalence was concluded based on the 90% confidence intervals of the Test/Comparator geometric means ratio of AUC0-t and Cmax, which must fall within range 80.00-125% [15,18]

The medical examination was performed within 21 days prior to first dosing day. The selection of study population were assessed with subject who fulfilled following parameters: medical history check, vital signs checking (blood pressure, pulse rate, respiratory rate, body temperature), physical examination, liver function test (AP, ALT, AST, and total/direct bilirubin), renal function (serum creatinine and ureum), routine hematology (hemoglobin, hematocrit, erythrocyte count, leucocyte count,

and platelet count), routine urinalysis (urine chemistry and urine sediment), blood electrolyte (sodium, potassium, and chloride), immunology test (hepatitis B surface antigen-HBsAg, antihepatitis C virus, and anti-human immunodeficiency virus - HIV, blood glucose, alcohol urine test, urine test for drug abuse (amphetamine, benzodiazepines, cannabinoids, and morphine), and ECG. Pregnancy screening (for women) was also tested during screening and prior to dosing in each period.

The participated subjects fulfilled the following criteria: able to participate, communicate well with the investigators and willing to provide written informed consent to participate in the study; healthy male and female subjects with absence of significant disease or clinically significant abnormal laboratory values on laboratory evaluation, medical history or physical examination during screening and could be considered healthy based on the evaluation; Aged 18-55 years; Preferably non-smoker or smoke less than 10 cigarettes per day; Body Mass Index (BMI) within 18.5-30.0 kg/m2; had normal vital signs after 10 minutes rest (systolic blood pressure: 100-129 mmHg; diastole blood pressure: 60-80 mmHg; pulse rate: 60-90 bpm).15,18

The subject with following criteria will not be recruited: history of allergy or hypersensitivity or contraindication to cephalexin or other members of the cephalosporin class of antibacterial drugs; pregnant or lactating female (urinary pregnancy test was applied to female subjects at screening and before taking the study drug); any major illness in the past 90 days or clinically significant ongoing chronic medical illness; presence of any clinically significant abnormal values during screening e.g. significant abnormality of liver function test (AST, ALT, alkaline phosphatase, total bilirubin, direct bilirubin ≥ 1.5 ULN), renal function test (serum creatinine concentration >1.4 mg/dL and ureum ≥ 1.5 ULN); positive Hepatitis B surface antigen (HBsAg), anti-HCV, or anti-HIV; clinically significant hematology abnormalities; clinically significant electrocardiogram (ECG) abnormalities; any surgical or medical condition (present or history) which might significantly alter the absorption, distribution, metabolism or excretion of the study drug, e.g. gastrointestinal disease including gastric or duodenal ulcers or history of gastric surgery; past history of anaphylaxis or angioedema; history of drug or alcohol abuse within 12 months prior to screening for this study; participation in any clinical trial within the past 90 days calculated from the last visit; history of any bleeding or coagulative disorders; history of difficulty with donating blood or difficulty in accessibility of veins in left or right arm; donation or loss or significant blood loss within 3 months before this study's first dosing day; intake of any prescription, non-prescription drug, food supplements or herbal medicines within 21 days of this study's first dosing day.

Prior to drug administration, randomization process was conducted. Each subject administered the test drug (T) and the comparator drug (R) according to one of two sequences (TR or RT). The randomization code was tabulated for all subjects based on block randomization with a block size of 4. The 6 permutations obtained from block size 4 with 2 sequences (TR and RT) were randomly assigned using Table of Random Numbers from Dixon & Massey, 1969, page 449, column 28 row 8 (read downward). The study drugs were dispensed by an independent person who had qualifications as a pharmacist prior to the dosing day. The randomization code was blinded for bioanalytical and statistical department [20].

RESULTS

Study procedures

Study drugs were reconstituted within 24 hours prior to dosing administration. Reconstituted study drugs were stored in refrigerator (2-8°C) until dosing process. One day before drug administration, all subjects arrived at PT Equilab International. Alcohol urine test and urine test for drug abuse (amphetamine, benzodiazepines, cannabinoids, and morphine) were performed for each subject. For female subjects, pregnancy test was also performed to make sure there was no pregnant subject enrolled in this study. Subjects were requested to fast from any food and drink except mineral water 10 hours before dosing. Mineral water was prohibited 1 hour prior and after drug administration, except that given at drug administration. In the morning of the dosing day, a 10 mL pre-dose pharmacokinetic blood sample was taken. Afterwards, the subjects were administered with either 5 mL suspension of the test drug or 5 mL suspension of the comparator drug. The study drugs were given started at approximately 07:00 AM with 150 mL of water. After drug administration, 5 mL post-dose blood samples were taken at 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 4.00, 5.00, and 6.00 hours at each period. Blood samples were collected in polyethylene tubes containing K3EDTA by using needle (21G for pre-dose and 22G for post-dose) for each period. The collected blood samples were centrifuged at 1538 g corresponding to 4000 rpm (radius of rotor=86 mm) for 15 minutes within 60 minutes after blood collection to get separated plasma samples. All plasma samples were stored in a freezer of 20°C ± 5°C until assayed. All activities were repeated in second period after interspaced 7 days of washout period.

During sampling days, meals and beverages provided were standardized. Xanthine-containing meals or beverages and fruit juices were not allowed for 48 hours before and during the entire sampling days. Consumption of alcohol-based products was restricted for 48 hours before and during the entire sampling days. All subjects were requested to remain seated in upright position for the first 4 hours after drug administration. Subject's wellbeing including vital signs (blood pressure, pulse rate, respiration rate, body temperature, and adverse events) was monitored at pre-dose, 2.00, 4.00, and 6.00 hours after drug administration. Subjects were suggested to inform the adverse events throughout the study. Standardized lunch was provided at approximately 4 hours after drug administration. The content and quantity during each study were same. The follow-up procedures were completed within 7 days after the last blood sampling.

Bioanalytical method: The cephalexin concentrations in plasma were assayed using a fully validated high performance liquid chromatography with ultraviolet detector (HPLC-UV) with respect to adequate sensitivity, selectivity, linearity, accuracy and precision (both within and between days). Stability of samples were performed under frozen conditions, at room temperature,

and during freeze-thaw cycle. Summary validation method of cephalexin in plasma is presented in Table 1.

Parameters	Conditions	Concentrations				
		LLoQ QC	Low QC	Medium QC	High QC	ULoQ QC
		251.48 ng/mL	754.44 ng/mL	17100.64 ng/mL	27159.84 ng/mL	35207.20 ng/mL
Precision	Intra-assay (% CV)	19.38%	5.91%	0.91%	0.73%	1.61%
	Inter-assay (% CV)	14.45%	5.52%	1.42%	1.82%	3.22%
Accuracy	Intra-Assay (% diff)	12.76%	2.52%	1.35%	-0.99%	0.40%
	Inter-assay (% diff)	2.97%	-0.51%	0.34%	-2.04%	-1.88%
Stability	Short term stability at room temperature for 6 hours	-	-2.83%	-	-3.46%	-
	Long term stability at 20 ± 5 °C for 65 days	-	-7.70% to -1.59%	-	-8.50 to -2.96%	-
	Freeze/ thaw cycle stability at -20 ± 5 °C for 4 cycles	-	-7.70% to 0.45%	-	-12.54 to -2.96%	-
	Post Preparative stability with reinjection for 57 hours	-	-6.62% to -2.62%	-	-8.47 to -4.61	-
Selectivity	For all 8 different blanks, the retention time regions of cephalexin as analyte and cefadroxil as internal standard were free from endogenous interfering peaks					
Carryover	After injecting the blank plasma samples after ULoQ, the % interference of analyte and internal standard were 0.00%					
Dilution Integrity	½ dilution (%diff & CV)	With % diff -3.95% and % CV 2.01%				
	¼ dilution (% diff & CV)	With % diff -4.25% and % CV 1.23%				
Concomitant Medication effect	For all 8 different blanks with presence of mefenamic acid & paracetamol as the concomitant medication, the retention time regions of cephalexin as analyte and cefadroxil as internal standard were free from interfering peaks.					

Table 1: Summary Validation Method of Cephalexin in Plasma.

Sample preparation and chromatography method: Plasma samples containing cephalexin were added cefadroxil as the internal standard and then extracted using protein precipitation with trichloroacetic acid 10%. The supernatant was separated into vial. An aliquot of 20 µL was injected into the HPLC-UV detection, with wave length 260 nm (Waters Alliance, Waters Corporation, Milford, USA). The signal was recorded by software Empower 3, Waters. Cephalexin concentrations were quantified by the internal standard method. Cephalexin chromatography was performed on reversed-phase column Symmetry C8 µm; 3.9 x 150 mm from Waters. Mobile phase was KH2PO4 20 mM pH ± 2.6 : acetonitrile. The chromatographic separation was gradient performed at flow-rate 1 mL/minute. The calibration curve was prepared by least square linear regression (Y=aX + b; where X was the concentration of cephalexin, and Y was the peak area ratio of cephalexin to cefadroxil).

Pharmacokinetic analysis: Pharmacokinetic parameters assessed in this study were maximum observed plasma concentration (Cmax), area under plasma concentration curve from administration to last observed concentration at time t (AUC0-t), area under plasma concentration vs time curve extrapolated to infinite time (AUC0-inf), time to reach Cmax (tmax), terminal phase half-life time (t½). Cmax and tmax were obtained directly from the observed data. The AUC0-t was calculated by the trapezoidal method. The AUC0-inf was calculated as AUC0-t + Ct/ke, where Ct is the last quantifiable concentration; ke is the terminal elimination rate constant and will be determined by least squares regression analysis during the terminal log-linear phase of the concentration-time curve. The t½ was calculated as 0.693/ke.

The statistical method for testing bioequivalence is ANOVA for 2-period, 2-sequence, 2-treatment cross-over comparing AUC0-t and Cmax after ln transformation of the original values. The terms to be used in the ANOVA model are sequence, subject

within sequence, period, and formulation. Bioequivalence is concluded if the 90% confidence interval of the test drug/reference drug geometric means ratio falls within the range of 80.00-125.00% with 80% power and 0.05 alpha, for AUC0-t and Cmax. Phoenix® WinNonlin® Version 8.2 (Certara L.P., St. Louis, MO, USA) was used to perform the statistical analyses of AUC0-t and Cmax using analysis of variance (ANOVA) after transformation of the data to their natural logarithmic (ln) values. The tmax were compared using non-parametric test from the original data using Wilcoxon matched-pairs test. The t½ difference was analyzed using Student's paired t-test or Wilcoxon matched-pairs test depending whether the differences of the paired data were distributed normally or not (Table 2).

Demographic Characteristic	Statistics	Subjects(N = 20)
Age (years)	Mean ± SD	32.45 ± 8.89
	Range	19 – 48
Gender, n (%)	Male	9 (45.00%)
	Female	11 (55.00%)
Race, n (%)	Indonesian	20 (100.00%)
	Other	0 (0.00%)
Body weight (kg)	Mean ± SD	56.45 ± 8.76
	Range	43.0 - 84.0
Body height (cm)	Mean ± SD	157.85 ± 7.41
	Range	144.0 - 168.0
Body Mass Index	Mean ± SD	22.64 ± 2.99
	Range	18.99 - 29.76
Smoke, n (%)	Non-smoker	16 (80.00%)
	Smoke < 10 cig./day	4 (20.00%)

Table 2: Summary of Demographic Data of Study Subject.

All 20 invited subjects were enrolled. One subject was dropped out prior to dosing period 1 due to positive drug abuse test. Hence, only 19 subjects were administered in period 1. Prior to dosing period 2, one subject was dropped out due to positive for urine pregnancy test. Only 18 of 20 subjects were completed the study. The summary of demographic data of the study subject was presented on Table 2.

The very common adverse events (≥ 10.00%) reported in this bioequivalence study were hematocrit decreased and urinary RBC increased. Both of them occurred in 15% of study subjects. All of the adverse events were found during Follow-Up Visit. Subjects were invited to refollow up their laboratory result. Six of thirteen cases were resolved, while seven cases were unknown since the subjects were lost to follow-up. All of the cases were mild and considered unrelated to the study drug (Table 3).

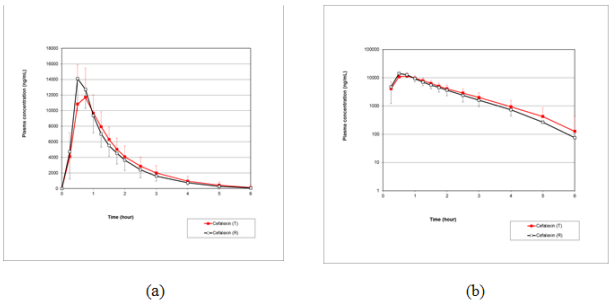
Parameter	Arithmetic mean (SD)	
	Test drug	Comparator drug
Cmax (ng.mL-1)	13305.52 (3290.83)	14920.71 (3404.05)
AUC0-t (ng.h.mL-1)	19622.05 (5020.31)	19124.08 (3388.27)
AUC0-inf (ng.h.mL-1)	20266.80 (5447.63)	19681.35 (3422.48)
t½ (h)	0.92 (0.22)	0.91 (0.16)
tmax (h)*	0.75 (0.50 – 1.25)	0.50 (0.50 – 0.75)

*median (range)

Table 3: Summary Pharmacokinetic Parameters of Cephalexin.

The pharmacokinetic and statistical analyses cephalexin in plasma were calculated from 18 completed subjects. The geometric means ratio of test drug / reference drug (90% confidence interval) of AUC0-t and Cmax were 101.34% (97.48-105.35%) and 88.78% (80.73-97.64%). The intra-subject coefficient of variation in this study was 6.68% for AUC0-t and 16.45 for Cmax. The summary of pharmacokinetic parameters of cephalexin is appeared in Table 3.

Statistical comparison of tmax of cephalexin was carried out on non-transformed data. Based on Wilcoxon matched-pairs test, tmax of test and comparator drugs were significantly different because the smaller rank sum for drug between the two formulations (negative values=0) was smaller than the critical value (Tvalue=2). Hence, in this study, test drug was absorbed slower than comparator drug. Statistical comparison of t½ of cephalexin was analyzed using Student's paired t-test since the differences of the paired data were normally distributed (tested with Kolmogorov-Smirnov with p=0.730). The t½ of test and comparator drugs were found not to be significantly different as the pvalue was 0.802, larger than 0.05 demonstrating a comparable rate of drug elimination from the body (Figure 2).



(a) (b)

Figure 2: Mean Plasma Concentration-Time Profiles of Cephalexin in linear (a) and semi-logarithmic scale (b).

DISCUSSION

The aim of the present study was to compare the bioavailability of Cefalexin 250 mg powder for oral suspension (Imexpharm

Corporation, Vietnam) as the test drug with Cefalexin 250 mg/5 mL granules for oral suspension (Flynn Pharma Ltd., Ireland) as the comparator drug.

This was an open-label, single-dose, randomized, two-period, two-sequence cross-over study under fasting condition which included 20 healthy adult male and female subjects. One subject was dropped out before dosing at period 1 due to positive drug abuse test and one subject was dropped out before dosing at period 2 due to positive urine pregnancy test. Eighteen subjects who completed the study were analyzed for bioequivalence calculation of cephalexin.

AUC0-t and Cmax of cephalexin were defined as the main parameters in order to assess possible bioequivalence between both preparations. Based on standard bioequivalence guideline, the criteria for bioequivalence were the 90% confidence interval of the test/comparator-geometric means ratio in the range of 80.00 125.00% for the AUC0-t and Cmax.

The geometric mean ratios (90% confidence intervals) of the test drug/comparator drug for cephalexin were 101.34% (97.48-105.35%) for AUC0-t and 88.78% (80.73-97.64%) for Cmax. The 90% confidence intervals of the test/comparator ratios for AUC0-t and Cmax of cephalexin were within the acceptance range for bioequivalence [14,17,18].

The AUC0-t value of cephalexin were more than 80% compared to the value of AUC0inf, (range of AUC0-t/AUC0-inf 93.21% to 97.37% for the test drug and 95.63% to 97.32% for the comparator drug), indicating that the sampling time was sufficiently long to ensure an adequate description of the absorption phase for cephalexin.

The mean (SD) elimination half-lives (t½) of cephalexin for the test drug was 0.92 (0.22) hours and for the comparator drug was 0.91 (0.16) hours. The half-life values of the test and the comparator drug were calculated utilizing Student's paired t-test and the result were not significantly different, demonstrating a comparable rate of drug elimination from the body.

The median (range) of the time to reach maximum cephalexin plasma concentration (tmax) of the test drug was 0.75 (0.50-1.25) hours and 0.50 (0.50-0.75) hours for the comparator drug. The tmax values of the two drugs (test and comparator drugs) were calculated using Wilcoxon matched-pairs test on the original data and the result were significantly different, demonstrating that the absorption of test drug was slower than of the comparator drug. Although tmax of test drug was slower than of comparator drug, the maximum plasma concentration (Cmax) of test drug itself was concluded equivalent to Cmax of comparator drug. From the guidelines, statistical evaluation of tmax is not required, as neither clinically relevant release claimed nor onset of action related to adverse events occurred for this study. Therefore, their efficacy was expected to be similar.

In the present study, the intra-subject coefficient of variance (%CV) obtained from the ANOVA for cephalexin AUC0-t and Cmax were 6.68% and 16.45%, respectively. Hence, the number of subjects who completed in this study, 18 subjects, was adequate to ensure that this study has an adequate power of the study to confirm a statistical conclusion.

CONCLUSION

In conclusion, the Cefalexin 250 mg powder for oral suspension (Imexpharm Corporation) is bioequivalent to the Cefalexin 250 mg/5 mL granules for oral suspension (Flynn Pharma Ltd., Ireland) when administered under fasting condition in healthy subjects.

REFERENCES

1. Beta lactam antibiotics. 2020.
2. Fernandes R, Amador P, Prudêncio C. β-Lactams: chemical structure, mode of action and mechanisms of resistance. Rev. Med Microbiol. 2013;24: 7-17.
3. Cephalosporine. 2020.
4. National Center for Biotechnology Information. 2020.
5. CoA RS Cephalexin USP.
6. Gower PE, Dash CH Cephalexin: human studies of absorption and excretion of a new cephalosporin antibiotic. Brit J Pharmacol. 1969;37(3): 738-747.
7. Khan MN, Ahmad J, Jan MN, Gulab H, Idrees M Development and Validation of a New Spectrophotometric Method for the Determination of Cephalexin Monohydrate in Pure Form and Pharmaceutical Formulations. J Braz Chem Soc. 27(5): 919-924.
8. Cephalexin. 2020.
9. Keflex tablets, Capsules and Granules. 2011.
10. Cefalexin 500mg Capsules. 2015.
11. RxList Keflex. (Cephalexin): drug description, indication & dosage, side effect & drug interactions, warning & precautions, overdosage & contraindications. clinPharmacol. 2017.
12. Cefalexin 250 mg/5 mL Ireland. 2018.
13. Lu Y, Chow SC, Zhu S. In vivo and In vitro Bioequivalence Testing. J Bioequiv Availab. 2014;6: 67-74.
14. Setiawati E, Deniati SH, Yunaidi DA, Handayani LR, Harinanto G, Santoso ID, et al. Bioequivalence Study with Two Naproxen Sodium Tablet Formulations in Healthy Subjects. J Bioequiv Availab. 2009;1(1): 28-33.
15. Badan Pengawas Obat dan Makanan. Pedoman Uji Bioekivalensi. Jakarta: BPOM. 2015.
16. World Medical Association Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects, last amended by the 64th WMA General Assembly, Fortaleza, Brazil, October. 2013.
17. Badan Pengawas Obat dan Makanan. Pedoman Cara Uji Klinik yang Baik. Jakarta: BPOM. 2015.
18. European Medicines Agency. Guideline on the Investigation of Bioequivalence. London: European Medicines Agency. 2010.
19. ASEAN. ASEAN Guideline for the Conduct of Bioequivalence Study. Lao PDR: ASEAN; 2015.
20. Dixon WJ, Massey FJ. Introduction to Statistical Analysis. 1969.