تعیین فراهمی زیستی نسبی نمونه‌های متفاوت کپسول سفالکسین

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چکیده:

سفالکسین یکی از سفالوسپورین‌های نسل اول با کاربرد بالینی فراوان می‌باشد که بصورت‌های مختلف تجویز می‌گردد، در تجویز خوراکی، این دارو بسرعت جذب شده و به میزان وسیعی در اکثر بافت‌ها ومایعات بدن توزیع می‌شود، بیش از ۹۰٪ سفالکسین بصورت داروی تغییر نیافته از طریق کلیه‌ها دفع می‌گردد. با توجه به تنوع در فرمولاسیون فرم خوراکی سفالکسین در ایران و تنوع در منابع خرید مواد اولیه آن، بررسی فراهمی زیستی نسبی این فرمولاسیون‌ها و مقایسه آنها با یک نمونه خارجی ضروری به نظر می‌رسد.

در این مطالعه از هشت داوطلب مرد سالم و چهارنمونه متفاوت کپسول سفرادین ساخت دو کارخانه داخل کشور (نمونه‌های *J.I,J.II,L.I,L.II*) و یک نمونه خارجی ساخت کارخانه *Lilly* انگلستان با نام تجارتی *Keflex* و به طریق متقاطع استفاده گردید. غلظت سفالکسین در هریک از نمونه‌های خونی و ادراری داوطلبان پس از هر تجویز به روش سنجش میکروبی آنتی‌بیوتیک‌ها و با استفاده از متد انتشار در دیسک تعیین گردید.

با استفاده از منحنی‌های پلاسمایی و ادراری رسم شده برای سفالکسین پارامترهای مختلف فارماکوکینتیکی و فراهمی زیستی نسبی آن محاسبه گردید. نتایج ادراری بدست آمده تأیید کننده نتایج خونی بود. بررسی‌های انجام شده نشان داد که نتایج بدست آمده در توافق کامل با نتایج گزارش شده در مقالات مختلف بود. کلیه پارامترهای فارماکوکینیتکی و هم‌ارزی زیستی نسبی محاسبه شده از داده‌های خونی و ادراری با استفاده از آزمون آماری مورد ارزیابی قرار گرفته و مشخص شد که این پارامترها برای نمونه‌های داخلی با نمونه خارجی مشابه می‌باشند. بدین ترتیب این مطالعه مشخص کننده هم‌ارز و معادل بودن (از نظر هر دو پارامتر میزان و سرعت جذب) نمونه‌های متفاوت کپسول سفالکسین ساخت داخل کشور با نمونه خارجی مورد بررسی می‌باشد و این نمونه‌ها هیچگونه تفاوت معنی‌داری با یکدیگر ندارند.

کلید واژه‌ها: ۱ـ سفالکسین ۲ ـ فراهمی زیستی ۳ـ پلاسما ۴ـ ادرار

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RELATIVE BIOAVAILABILITY OF CEPHALEXIN DIFFERENT BRANDS OF CAPSULES

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ABSTRACT

In a cross over study eight normal human volunteers were employed. The bioavailability of different commercial brands of cephalexin capsules were examined. The relative bioavailability of four brand (J.I,J.II,L.I,L.II) manufactured by two different domestic compa ies were compaired with one brand (Keflex) which was manufac ured by Lilly pharmaceutical company, England. The plasma and urine cephalexin concentration were determined by microbiological assay (disk diffusion) using Sarcina Lutea ATCC 9341 as test organism. Plasma and urine data were used to evaluate various pharmacokinetic parameters cephalexin including K, $t_{1/2}$, C1/F, Vd/F, T_{max}, C_{max} AUC and F (relative).

Results obtained from urinary data were supported the plasma data. The analysis of variance, to compare relative bioavailability and other pharmacokinetic parameters between tested samples were performed. These information indicates that there are no significant differences between the five different tested brands and they are bioequivalent. Therefore it can be suggested that brands (J.I,J.II,L.I,L.II) which formulated by domestic manufactures are bioequivalent and comparable to each other and to the one formulated by Lilly pharmaceutical company.

Key Words: *1) Cephalexin* *2) Bioavailability* *3) Plasma* *4) urine*

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INTRODUCTION

Cephalexin , (7R)-3-Methyl-7- (α-D-Phenylglycylamino) -3-Cephem-4-Carboxylic Acid Monohydrate, is a semisynthetic derivative of cephalosporine C.Cephalexin is bactericidal and has a broad spectrum of antimicrobial activity. It has weak bondability to blood protein, has no metabolites, has low toxicity, and is rapidly absorbed following oral administration to give a high serum level and urine concentration. Cephalexin is excreted unaltered by the kidneys, almost all of the dose being recovered within six hours [11].

In clinical chemotherapy the bioavailability of drugs is a very important subject. It is obvious that all commercially available products do not show bioequivalency. Therefore, the evaluation of the bioavailability of various solid dosage forms especially where the only generic products are available is necessary.

In the present study the relative bioavailability of four generic cephalexin capsules were examined. A known marketed cephalexin capsule (Keflex, Lilly, England) was used to compare the result of the study.

EXPERIMENTAL

Reagent and Materials: Cephalexin monohydrate used as standard material and a marketed cephalexin capsule (Keflex) which also used for comparison to other generic capsules were gifted from Jaber Ibn-Hayyan and Loghman pharmaceutical companies(Tehran,Iran). All the reagent used were Merk analytical grade.

Subjects and Treatments: Eight normal healthy male volunteers, 22-28 years old, weighing between 61-74 Kg participated in this study. The subjects had no past histories to allergic reaction to penicillin and showed normal renal function. All the subject had no concurrent drug treatment for several days before and during the study. Informed written consent was obtained from each subject. The overnight fasting subjects recieved a single permitted to eat until 3h after dosing. Five different dosage forms (JI, JII, LI, LII and Keflex) of cephradine on five separate occasions were tested. A Known commercial cephalexin capsule (Keflex, Lilly, Pharmaceutical Company, England), was used as standard to be compared with four local generic dosage forms, brand JI and JII, (Jaber Ibn - Hayyan Pharmaceutical Company, Tehran-Iran) and brand LI and LII,(Loghman Pharmaceutical and Hygenic Company, Tehran-Iran). At least one week separated all experiments. The study was designed as a randomized double - blined complete crossover investigation.

Sampling: Venous blood samples were collected into heparinized glass tubes immediately prior to dosing, and at 0.5,1,1.5,2,3,4,5,6 and 8 hours after drug

administration. Total urine voids were collected for the following time period after drug administration: 0-1, 1-2, 2-3, 3-4, 4-6, and 6-8 hours. Plasma separated from all blood samples immediately after collection and frozen until the time of analysis. Urine volume was measured and an aliquot was frozen for analysis.

Assay: Plasma and urine sample concentrations were measured by disc diffusion microbiological assays using Sarcina Lutea ATTC 9341 as the test organism. Standard curves for each biological fluid sample were freshly prepared on each day of analysis, using human plasma or a phosphate buffer as the diluent. The lower limit of sensitivity for the cephalexin assay was 0.25 mcg/ml.

Pharmacokinetic Analysis: Plasma and urine data were analysed for appropriate pharma -cokinetic parameters using a one compartment open model with first-order absorpation [4,8]. Area under the cephalexin plasma concentration versus time curves (AUC) were calculated for all subjects using trapezoidal method. Other pharmacokinetic parameters such as the peak concentration, time of peak concentration, clearance elimination half-life and urinary recovery were calculated and compared for the various dosage forms. The relative bioavailability of various dosage forms were compared using urine and plasma data.

RESULTS AND DISCUSSION

Plasma data: Figure 1 shows the plasma concentration of cephalexin (average of

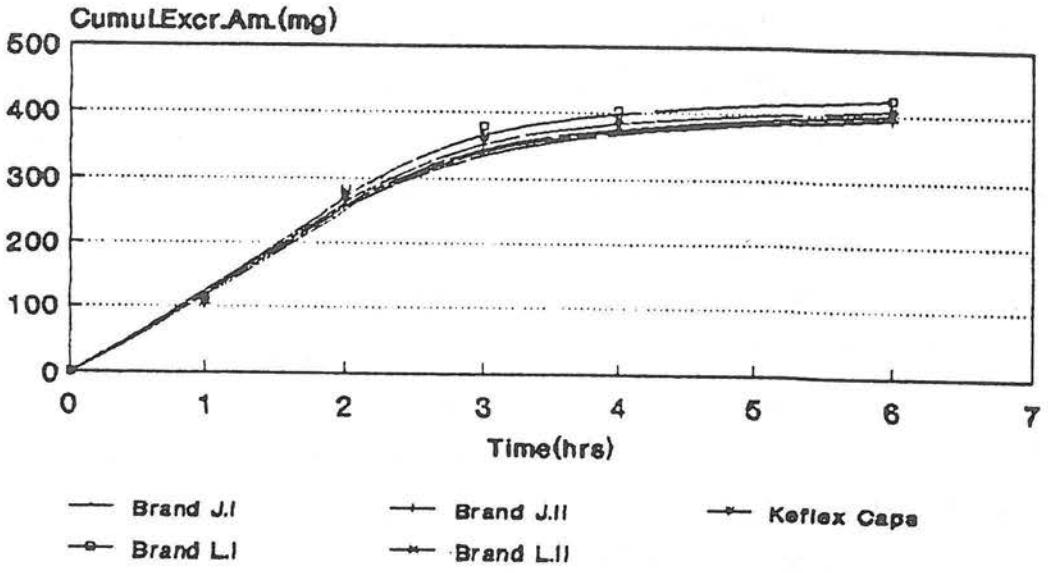

Figure 1. Comparison of Mean Cumul. Urinary Excre. of cephalexin after Oral Administration of 500 mg of Each Brands in 8 Subjects

eight subjects) for five different dosage forms(Keflex, JI,JII,LI,LII). These results indicate that these profiles are very similar. Pharmacokinetic parameters which have been utilized as a function of the rate of drug absorption are the peak plasma concentration and time of peak plasma concentration[12]. The mean time of peak plasma concentration (Tmax) for all brands and subjects was 1.12±0.11 h (table.1)

Table 1: Mean Pharmacokinetic Parameters of Cephalexine after Oral Administration of Various Cephalexine Capsules to Eight Subjects

BRAND	K	T 1/2	CL/F	V/F	Tmax	Cmax	AUC(0 __ ∞)
	(l/h)	(h)	L/h	(L)	(h)	(μ g/mL)	(μ g/mL)
Keflex	0.64	1.1	18.3	28.6	1.1	16.2	28.3
J.I	0.63	1.1	21.4	33.6	1.1	14.3	24.4
J.II	0.66	1.1	18.4	28.1	1.1	15.0	28.6
L.I	0.60	1.2	16.2	27.2	1.1	18.1	32.0
L.II	0.67	1.0	18.3	27.3	1.3	13.3	28.5
Mean±S.D	0.64±0.03	1.1±0.1	18.5±1.8	29.0±2.7	1.1±0.1	15.4±1.8	28.4±2.7

which is in agreement with other reports [1,7,9,13]. Mean peak plasma concentration (Cmax) for all tested brands and subjects were 15.40±1.85 mcg/ml (table 1). This value agrees with other reports [3,7,9,10,13]. Statistical analysis of the Cmax and Tmax data indicated no significant differences (p=0.05) between different brands and subjects. Other pharmacokinetic parameters of cephalexin were calculated using individual data after administration of various dosage forms (table 1). All the pharmacokinetic parameter values are in agreement with the data reported in the literature [7,9,13]. Statistical analysis of these data showed no significant differences (p=0.05) between the pharmacokinetic parameters of five different tested dosage forms. The extent of absorption of various dosage forms evaluated using area under the plasma concentration-time curve (AUC), (table 1). The relative bioavailability (Keflex, used as standard, 100% availability assumed) of all tested brands is shown in table 2. No statistically significat differences (p=0.05) between the different brands of cephalexin capsules were observed. However significant inter subject variation was

observed table 2.

Table 2: Relative Bioavailability of Five Different Cephalexine Capsules

BRAND	SUBJECTS								Mean(±S.D.)
	S.K.	J.E.	M.SH.	M.R.	A.R.	N.B.	A.H.	M.K.	
Keflex	100	100	100	100	100	100	100	100	100(.....)
J.I	131	109	60	59	75	82	103	95	89.2(±25.0)
J.II	105	99	108	111	91	96	112	84	100.8(±10.0)
L.I	109	125	116	110	116	101	112	116	113.1(±7.0)
L.II	87	104	102	90	127	100	99	99	101.0(±12.02)

Urinary excretion of cephalexin: Since cephalexin is eliminated unchanged in the urine, the percentage of the total dose excreted can be used as indication of bioavailability [4,8]. Since the concetration of cephalexin in the urine sample collected at 8 hours showed negligible value, therefore the cumulative amount excreted after 6 hours would be a proper indication of the extent of cephalexin absorption. Figure 2

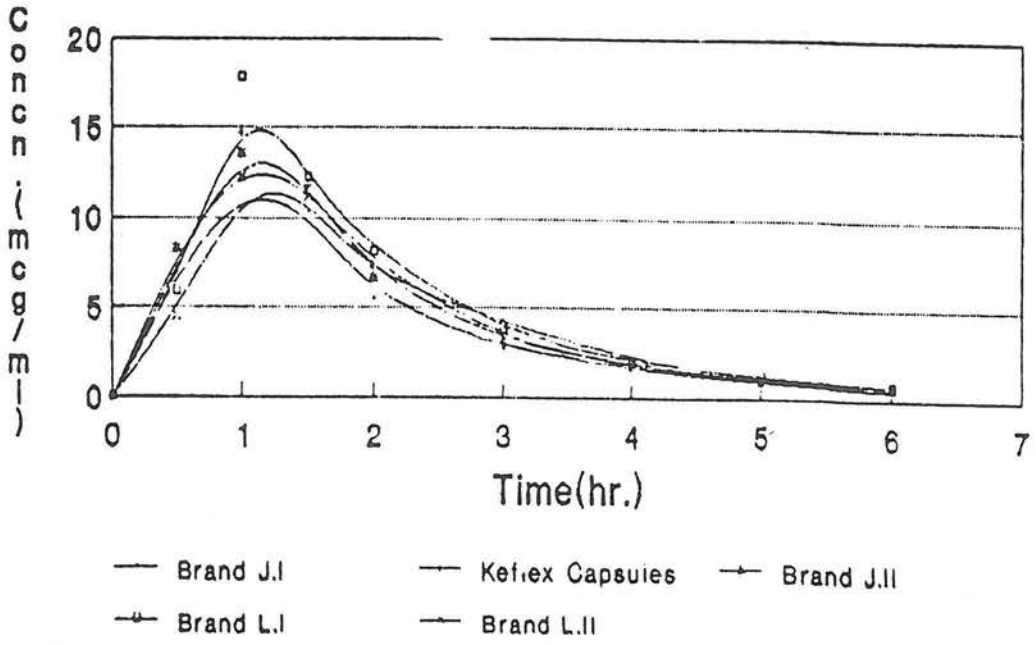

Figure 2. Comparison of Mean Plasma Cephalexin Concen. after Oral administration of 500 mg of Each Brands in 8 subjects

shows the mean cumulative cephalexin excreted after administration of five different brands. The mean value for percentage of administered dose excreted over the period

of 6 hours to eight subjects is 80.94 ± 2.44 (range from 78.76 to 84.84 %dose). which is similar to the other previously reported values [2,6,7]. No significant statistical differences (p= 0.05) between the different brands were observed. The relative bioavai -lability of various dosage forms were estimated using cumulative amount of unchanged cephalexin excreted. Analysis of variance of these data showed no significant statistical differences (p= 0.05) between the relative bioavailability of all tested brands. These results support the information obtained from plasma Data.

Comparison of plasma and urinary Data: The mean plasma half-life values of cephalexin in eight subjects after oral administration of five different brands of cephalexin capsules were calculated from urine data (0.81±0.01 hours) and from plasma data (1.1±0.05) which are farely in good agreement. Comparison of relative bioavailability the area under the plasma time curve (AUC), total urinary recovery of drug (%dose), Ae ∞ and other pharmacokinetic parameters clearly shows the results obtained from urinary data clearly support the information obtained from plasma data.

CONCLUSION

The plasma and urine data of this study demonstrate that the bioavailability and other pharmacokinetic parameters of cephalexin after single oral administration of five different dosage forms of cephalexin capsules. No significant statistical differences (p=0.05) can be demonstrated in any of the pharmacokinetic parameter measured at any of dosage forms used in this investigation when comparing the four different generic agents, (JI,JII,LI,LII) to a known marketed cephalexin capsule (Keflex). The urinary data was supported the plasma data in all cases.

The results of this study indicates that the behavior of different tested brands of cephalexin capsules are compatible and bioequivalent.

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REFERENCES

1) Braun,R., et al, Cephalexin and Cephaloglycin Activity in Vitro and Absorption and Urinary Excretion of Single Oral Dose in Normal Young Adults, Appl. Microbiol., (1968)., 16(11):1684-1694.

2) Bustrack,J.A., Lawson, L.A., Bauer, L.A., Wilson, D., and Foster, T., A Comparative Pharmacokinetic and Safety

Study of an Investigational Oral Cephalosporin, RMI 19,592, Curr. Ther.Res., (1980)., 28(2): 208-216.

3) Cadorniga, R., et al, Cephalexin Bioavailability, Comparative Study Between Single Capsulated Presentation and Cephalexin Plus Bromohexine Capsules and Suspsension, Proc. Eur. Congr. Biopharm. Pharmacokinet. 3rd, (1987)., 1:428-434.

4) Finkelstein,E.R., Quintiliani, R., Lee, C., Bracci and C.H., Nightingale, Pharmacokinetics of Oral Cephalosporins: Cephradine and Cephalexin, J. Pharm. Sci., (1978) .. 67(10): 1447-1450

5) Gower, P.E., Dash, C.H., Cephalexin : Human Studies of Absorption and Excretion of New Cephalosporin Antibiotic, Br.J.Pharmacol., (1969), 37: 738-747.

6) Griffith, R.S., Black, H.R., Cephalexin, Med. Clin. North Am., (1970)., 54(5): 1229-1244

7) Hatstein, A.I., et al, Comparison ot Pharmacological and Antimicrobial Properties of Cephadroxil and Cephalexin, Antimicrob. Ag. Chemother.,(1977), 12(1): 93-97

8) Nightingale , C.H., et al, Pharmacokinetics and Clinical Use of Cephalosporin Antibiotics, J.Pharm. Sci., (1975)., 64(12): 1899-1972

9) Perkin, R.L., et al, Cephalexin, In Vitro Bacterial Suseptibility, Absorption in Volunteers, and Antibacterial Activity of Serum and Urine, Am.J.Med.Sci.,(1968)., 256:122-129.

10) Pfeffer, M., et al, Comparative Human Oral Clinical Pharmacology of Cephadroxil, Cephalexine and Cephradine, Antimcrob. Ag. Chemother., (1977)., 11(2):331-338.

11) Reynolds, J.E., " Martindale, The Extra Pharmacopeia ", The Pharmaceutical Press, 30ed (1993).

12) Ritschel, W.A., " Handbook of Basic Pharmacokinetics " Drug Intelligence Publications, Inc., Hamilton, lst Ed(1971).

13) Thornhill, T.S., et al, In Vitro Antimicrobial Activity and Human Pharmacology of Cephalexin, A New Orally Absorbed Cephalosporin C Antibiotic, Appl. Microbiol., (1969), 17(3): 457-461.