تعیین فراهمی زیستی نسبی نمونه‌های متفاوت کپسول سفالکسین

علیرضا اسدالله شیرازی

صدیقه فضلی براز

محمد حسن زاده خیاط

چکیده:

سفالکسین یکی از سفاروضئورین‌های نسل اول یا کابرد بالینی فروآین می‌باشد که به‌صورت‌های مختلف تجویز می‌گردد. در تجویز خوراکی، این دارو بسرعت جذب شده و به میزان وسیعی در اکثر بافت‌ها و سایر بدن توزیع می‌شود. بخش از 90% 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 سفاروضئورین ساخت و بر اساس خاکمی داخل کشور Keflex (نمونه‌های I, I.I, I.I.I, I.I.I.I) و یک نمونه خارجی ساخت کارخانه اینگلستان با نام تجاری Lilly متقابل استفاده گردید. غلظت سفالکسین در هر یک از نمونه‌های خویش و ادرازی داوطلبان پس از هر تجویز به روش سنجش میکروبوی آنتی‌بیوتیک‌ها و با استفاده از متد انتشار در دیسک تعیین گردید.

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

کلید واژه‌ها: 1- سفالکسین
2- فراهمی زیستی
3- ادراز
4- پلاسمای

دانشکده داروسازی، دانشگاه علوم پزشکی مشهد

سال سوم / شماره ۱ و ۲ / بهار و تابستان ۱۳۷۵

۱۷۹ مجله دانشگاه علوم پزشکی ایران
RELATIVE BIOAVAILABILITY OF CEPHALEXIN DIFFERENT BRANDS OF CAPSULES

M.K. Hassanzadeh*  S. Fazli-Bazaz  A. Shirazie

ABSTRACT
In a cross over study eight normal human volunteers were employed. The bioavailability of different commercial brands of cephalxin capsules were examined. The relative bioavailability of four brand (I.I.I.I., L.I.I.) manufactured by two different domestic companies were compared with one brand (Keflex) which was manufactured by Lilly pharmaceutical company, England. The plasma and urine cephalxin 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 cephalxin including K, t\textsubscript{1/2}, C\textsubscript{1/F}, Vd/F, T\textsubscript{max}, C\textsubscript{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 (I.I.I., I.I.) which formulated by domestic manufactures are bioequivalent and comparable to each other and to the one formulated by Lilly pharmaceutical company.

Key Words: 1) Cephalxin  2) Bioavailability
3) Plasma  4) urine

* School of Pharmacy Mashhad University of Medical Sciences Mashhad 9775-1965, IRAN
INTRODUCTION

Cephalexin, (7R)-3-Methyl-7-(α-D-PHENYLGLYCICYLAMINO)-3-Cepham-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 (1).

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 received 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-blind 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 cephalaxin assay was 0.25 mcg/ml.

Pharmacokinetic Analysis: Plasma and urine data were analysed for appropriate pharmacokinetic parameters using a one compartment open model with first-order absorption\(^{(4,8)}\). Area under the cephalaxin 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 cephalaxin (average of

![Figure 1. Comparison of Mean Cumul. Urinary Excre. of cephalaxin after Oral Administration of 500 mg of Each Brands in 8 Subjects](image-url)
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**

<table>
<thead>
<tr>
<th>BRAND</th>
<th>(K) (L/h)</th>
<th>(T_{1/2}) (h)</th>
<th>(CL/F) (L/h)</th>
<th>(V/F) (L)</th>
<th>(T_{max}) (h)</th>
<th>(C_{max}) ((\mu) g/mL)</th>
<th>(AUC(0\rightarrow\infty)) ((\mu) g/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keflex</td>
<td>0.64</td>
<td>1.1</td>
<td>18.5</td>
<td>28.6</td>
<td>1.1</td>
<td>16.2</td>
<td>28.3</td>
</tr>
<tr>
<td>JI</td>
<td>0.63</td>
<td>1.1</td>
<td>21.4</td>
<td>33.6</td>
<td>1.1</td>
<td>14.3</td>
<td>24.4</td>
</tr>
<tr>
<td>JII</td>
<td>0.66</td>
<td>1.1</td>
<td>18.4</td>
<td>28.1</td>
<td>1.1</td>
<td>15.0</td>
<td>28.6</td>
</tr>
<tr>
<td>LI</td>
<td>0.60</td>
<td>1.2</td>
<td>16.2</td>
<td>27.2</td>
<td>1.1</td>
<td>18.1</td>
<td>32.0</td>
</tr>
<tr>
<td>LII</td>
<td>0.67</td>
<td>1.0</td>
<td>18.3</td>
<td>27.3</td>
<td>1.3</td>
<td>15.3</td>
<td>28.5</td>
</tr>
<tr>
<td>Mean±S.D</td>
<td>0.64±0.03</td>
<td>1.1±0.1</td>
<td>18.5±1.8</td>
<td>29.0±2.7</td>
<td>1.1±0.1</td>
<td>15.4±1.8</td>
<td>28.4±2.7</td>
</tr>
</tbody>
</table>

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 significant 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**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Keflex</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100(......)</td>
</tr>
<tr>
<td>J.I</td>
<td>131</td>
<td>109</td>
<td>60</td>
<td>59</td>
<td>75</td>
<td>82</td>
<td>103</td>
<td>95</td>
<td>89.2±25.0</td>
</tr>
<tr>
<td>J.II</td>
<td>105</td>
<td>99</td>
<td>108</td>
<td>111</td>
<td>91</td>
<td>96</td>
<td>112</td>
<td>84</td>
<td>100.8±10.0</td>
</tr>
<tr>
<td>L.I</td>
<td>109</td>
<td>125</td>
<td>116</td>
<td>110</td>
<td>116</td>
<td>101</td>
<td>112</td>
<td>116</td>
<td>113.1±7.0</td>
</tr>
<tr>
<td>L.II</td>
<td>87</td>
<td>104</td>
<td>102</td>
<td>90</td>
<td>127</td>
<td>100</td>
<td>99</td>
<td>99</td>
<td>101.0±12.02</td>
</tr>
</tbody>
</table>

*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 (48). Since the concentration 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 shows the mean cumulative cephalexin excreted after administration of five different brands. The mean value for percentage of administered dose excreted over the period

![Figure 2. Comparison of Mean Plasma Cephalexin](image)

*Concen. after Oral administration of 500 mg of Each Brands in 8 subjects*
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 (26,7). No significant statistical differences (p=0.05) between the different brands were observed. The relative bioavailability of various dosage forms were estimated using cumulative amount of unchanged cephalixin 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 cephalixin in eight subjects after oral administration of five different brands of cephalixin capsules were calculated from urine data (0.81±0.01 hours) and from plasma data (1.1±0.05) which are fairly 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.

REFERENCES


