تعیین فراهمی زیستی نسبی نمونه‌های متفاوت کپسول سفالسکسین

علیرضا اسدالله شیرازی

صدمی فضلی برزگ

چکیده:
سفالسکسین یکی از سفالسپوریون‌های نسل اول یا کاکرد بالینی فراوانی می‌باشد که بصورت‌های مختلف تجویز می‌گردد. در تجویز خوراکی، این دارو بسرعت جذب شده و به میزان وسیعی در اکثر باقی‌ها و مايعات‌بند تنوزیم می‌شود. بیش از 90% سفالسکسین بصورت داروی تغییر نیافته از طریق کلیه‌ها دفع می‌گردد. با توجه به تنویع در فرمولاسیون فرم خوراکی سفالسکسین در ایران و تنویع در منابع خرد مواد اولیه آن، بررسی فراهمی زیستی نسبی این فرمولاسیون‌ها و مقایسه آنها با یک نمونه خارجی ضروری به نظر می‌رسد.


با استفاده از منحنی‌های پلاسما و اداری رسم شده برای سفالسکسین باارتره‌ای مختلف فراماهوکینتیکی و فراهمی زیستی نسبی آن محاسبه گردید. نتایج اداری بدست آمده تا مده تنظیم 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 فراماهوکینتیکی و هماچه زیستی نسبی محاسبه شده از داده‌های خونی و اداری با استفاده از آزمون آماری موردنامه‌ی گزارش و مشخص شد که این پارامترهای برای نمونه‌های داخلی با نمونه خارجی مشابه می‌باشند. بدین ترتیب این مطالعه مشخص کننده مهم و معنادار بودن (از نظر هر دو پارامتر میزان و سرعت جذب) نمونه‌های متفاوت کپسول سفالسکسین ساخت داخل کشور با نمونه خارجی مورد بررسی می‌باشد و این نمونه‌ها هیچگونه تفاوت معنی‌داری با یکدیگر ندارند.

کلید واژه‌ها: ١- سفالسکسین
٢- فراهمی زیستی
٣- ادار

دانشگاه داروسازی، دانشگاه علوم پزشکی مشهد

سال سوم / شماره ١ و ٢ / بهار و تابستان ١٣٧٥

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

M.K. Hassanzadeh
S. Fazli-Bazazz
A. Shirazie

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 (I.I.I.I, I.I.I.I, I.I.I.I, I.I.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 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 \( K_{t_{1/2}} \), \( C_{1/F} \), \( Vd/F \), \( T_{\text{max}} \), \( C_{\text{max}} \), 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.I.I.I, I.I.I.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) Cephalexin 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-Phenylglycylamino)-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 was 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 subjects 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 cephadrine 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-blinded 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 cephalixin 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. Area under the cephalixin 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 cephalixin (average of
Relative bioavailability of cephalexin......

M.K. Hassanzadeh and et al

eight subjects) for five different dosage forms (Keflex, J.I, J.II, L.I, L.II). 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 \(1.12 \pm 0.11\) 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>Tmax (h)</th>
<th>Cmax (µg/mL)</th>
<th>AUC(0→∞) (µg/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>J.I</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>J.II</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>L.I</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>L.II</td>
<td>0.67</td>
<td>1.0</td>
<td>18.3</td>
<td>27.5</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 (\(^{17,9,13}\)). Mean peak plasma concentration (Cmax) for all tested brands and subjects were \(15.40 \pm 1.85\) 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>82</td>
<td>103</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>112</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 cephalaxin: Since cephalaxin is eliminated unchanged in the urine, the percentage of the total dose excreted can be used as indication of bioavailability (4,8). Since the concentration of cephalaxin 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 cephalaxin absorption. Figure 2 shows the mean cumulative cephalaxin 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 bioavailability of various dosage forms were estimated using cumulative amount of unchanged cephalaxin 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 cephalaxin in eight subjects after oral administration of five different brands of cephalaxin 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


CONCLUSION

The plasma and urine data of this study demonstrate that the bioavailability and other pharmacokinetic parameters of cephalaxin after single oral administration of five different dosage forms of cephalaxin 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 cephalaxin 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 cephalaxin capsules are compatible and bioequivalent.

ACKNOWLEDGMENT

This work supported by a grant from Jaber Ibn-Hayyan and Loghman Pharmaceutical Companies. The authors would like to thank the authorities in school of pharmacy Mashhad University of Medical Sciences for their cooperations.


