تعیین فراهمی زیستی نسبی نمونه‌های متفاوت کپسول سفالسین

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چکیده:

سفالسین یکی از سفالسوپرین‌های نسل اول با کاربرد بالینی فراوان می‌باشد که بصورت‌های مختلف تجویز می‌گردد. در تجویز خوراکی، این دارو به سرعت جذب شده و به میزان وسیعی در اکثر بافت‌ها و مایعات بدن توزیع می‌شود. پیش از ۹۰% سفالسین بصورت داروی تغیر نیافتگی از طریق کلیه‌ها دفع می‌گردد. با توجه به تنوع در فرمولاسیون فرم خوراکی سفالسین 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 متغیف کپسول سفرانی ساخت دو کارخانه داخل کشور Keflex (تولید های I,II,III,IV,VI,II) و یک نمونه خارجی ساخت کارخانه انگلستان با نام تجاری Lily (کنف برداری) متقابل استفاده گردید. غلظت سفالسین در هر کیل گرم نمونه‌های خونی و ادراری داوطلبان پس از هر تجویز به روش سنجش میکروبی آنتی‌بیوتیک‌ها و با استفاده از متر انتشار در دیسک تعمیم گردید.

با استفاده از منحنی‌های پلاساپای و ادراری رسم شده برای سفالسین پرامترهای مختلف فرامکوکینتیکی و فراهمی زیستی نسبی آن محاسبه گردید. نتایج ادراری بیانگر آمده که بسته به تغییر کننده نتایج خونی بود. بررسی‌های انجام شده نشان داد که نتایج بسته به تغییر کننده نتایج گزارش شده در مقالات مختلف بود. کلیه پرامترهای فرامکوکینتیکی و همانزی زیستی نسبی محاسبه شده از داده‌های خونی و ادراری با استفاده از آزمون آماری سورد ارزیابی قرار گرفته و مشخص شده که این پرامترها برای نمونه‌های داخلی با نمونه خارجی مشابه می‌باشد. بنابراین و بر اساس نتایج کلیه متغیرهای مربوط به فراهمی زیستی نسبی این نمونه‌های متفاوت کپسول سفالسین از دو کارخانه داخل کشور با نمونه‌های خارجی مورد بررسی می‌باشد و این نمونه‌ها هیچگونه تفاوت معنی‌داری با یکدیگر ندارند.

کلید واژه‌ها: ۱- سفالسین
۲- فراهمی زیستی
۳- ادرار
۴- پلاساپای

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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 (I, II, III, IV) manufactured by two different 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 $K, t_{1/2}, C_{1/F}, Vd/F, T_{max}, C_{max}, AUC$ 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 (I, II, III, IV, V) 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

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 bioavailabil-
ity of four generic cephalixin capsules were
examined. A known marketed cephalixin
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 cephalixin 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 cephalixin 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 ATCC 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 pharmacokinetic parameters using a one compartment open model with first-order absorption (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
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±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>T1/2 (h)</th>
<th>CL/F (L/h)</th>
<th>V/F (L)</th>
<th>Tmax (h)</th>
<th>Cmax (µ g/mL)</th>
<th>AUC(0-∞) (µ 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>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>27.3</td>
<td>1.3</td>
<td>13.3</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>
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<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\(^{(4,8)}\). 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

![Graph](image-url)

Figure 2. Comparison of Mean Plasma Cephalexin
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 \(^{6,7}\). 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 \((1.1±0.05\) hours\) which are rarely in good agreement. Comparison of relative bioavailability the area under the plasma time curve \((AUC)\), total urinary recovery of drug \(\%\dose\), \(Ae\infty\) and other pharmacokinetic parameters clearly shows the results obtained from urinary data clearly support the information obtained from plasma data.

**REFERENCES**


