Pharmacokinetics of cefixime in the young and elderly

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The pharmacokinetics of cefixime were compared in 12 young and 12 elderly subjects receiving 400 mg once-a-day for five days. Mean peak serum concentrations (Cmax) on days one and five in the elderly (4.90 and 5.68 mg/l) were comparable (P > 0.05) to those in the young subjects (3.88 and 4.74 mg/l). Serum area under the curve (AUC) values on days one and five in the elderly (41.0 and 49.5 mg • h/l) were higher (P < 0.05) than those in young subjects (28.6 and 34.9 mg • h/l). In addition, the elimination half-life, mean residence time, average concentration, minimal concentration and renal clearance (Clr) values were significantly higher (P < 0.05) in the elderly. A significant linear correlation (P < 0.05) was found between the Clr of cefixime (total and unbound) and creatinine clearance. The urinary recovery (Ae) and protein binding of cefixime on days one and five was similar in the elderly and young. Overall, there is no need for any dosage adjustment of the drug in the elderly.

Introduction

Cefixime is a new orally active cephalosporin antibiotic (Figure 1) that differs in structure from other oral cephalosporin antibiotics in that it possesses a vinyl group in the 3-position of the aminothiazolyl ring and a β-2-aminothiazolyl-4-yl-(α-alkoximine) acetamido side chain at the 7-position of the basic cephem molecule. These structural modifications result in cefixime having good oral absorption, stability against inactivation by β-lactamase enzymes and excellent antibacterial activity against common clinical isolates, including Proteus mirabilis, Proteus vulgaris and Providencia stuartii, Streptococcus pneumoniae, Haemophilus influenzae, Branhamella catarrhalis, Neisseria gonorrhoeae and N. meningitidis, Escherichia coli and Klebsiella pneumoniae and K. oxytoca (Pfeffer et al., 1977; Kamimura et al., 1984; Neu, Chin & Labthavikul, 1984; Shigi et al., 1984; Brittain et al., 1985; Fuchs et al., 1986). It is useful in the treatment of otitis media in children (McLinn, 1987) and urinary and respiratory tract infections in children (Risser et al., 1987) and adults (Levenstein et al., 1986; Kiani et al., 1988; Irvani et al., 1988).

Thus far, the pharmacokinetic profile of the drug has been studied in young male volunteers in the 18–35 year age range. The objective of the present study was to compare the pharmacokinetic profile of the drug in an older population with that in young subjects following single and multiple oral dosing.

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Materials and methods

Subjects

All subjects gave written informed consent, were healthy, active, ambulatory adults with no evidence of medical disease and did not receive other medications. Approval for the study was given by the institution's Human Research Committee. Table I contains pertinent demographic data. General physical examination and laboratory analyses were conducted before and after the study. All subjects were housed in a clinical research facility (Bio-Research Clinical Research Centre, Montreal, Quebec, Canada) for the duration of the study.

Each of the subjects received a single 400 mg oral dose of cefixime (as two 200 mg capsules; Fujisawa Pharmaceutical Co., Osaka, Japan) once daily in the morning for five days. On days one and five, the drug was given after an overnight fast, and subjects were then fasted for an additional 4 h after dosing. Doses were given with 240 ml of water. On study days two, three and four, subjects received the oral dose with a standard breakfast.

Venous blood samples (2 ml each) were drawn by venipuncture into siliconized blood collection tubes before (0 h) and at 1, 2, 3, 4, 5, 6, 8, 12, 16 and 24 h on days one and five, and just before dosing on days three and four. Additional blood samples (8 ml) were collected before (0 h) and at 4 and 12 h after dosing on days one and five for protein binding determinations. Serum was separated by centrifugation and stored frozen (≤ −20°C) until assay. Urine samples were obtained from complete collections made for 2 h before (0 h) and at 0-2, 2-4, 4-6, 6-8, 8-12 and 12-24 h intervals on days one and five. Additional 24 h urine collections were obtained on days two, three and four. For each collection, urine volume and pH were recorded and an aliquot was stored frozen (≤ −20°C) until assay.

Protein binding determination

The protein binding of cefixime in serum samples obtained from each subject before (0 h) and at 4 and 12 h after drug administration on days one and five was determined

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Age (years)</th>
<th>Weight (kg)</th>
<th>Creatinine clearance (Cl&lt;sub&gt;K&lt;/sub&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>mean range</td>
<td>mean range</td>
<td>mean range</td>
</tr>
<tr>
<td>Young</td>
<td>12</td>
<td>22-8 (20-32)</td>
<td>70-8 (58-9-89-5)</td>
<td>101 (76-140)</td>
</tr>
<tr>
<td>Elderly</td>
<td>12</td>
<td>68-9 (65-74)</td>
<td>75-8 (66-0-93-4)</td>
<td>81 (68-100)</td>
</tr>
</tbody>
</table>
Pharmacokinetics of cefixime in young and elderly

by an established equilibrium dialysis method for cefixime (Bialer et al., 1986). To each of the predose (0 h) serum samples was added 3 mg/l of cefixime. Duplicate aliquots (0.5 ml) of each serum sample were dialyzed against isotonic sodium phosphate (0.1 M)-sodium chloride (0.25%) buffer (pH 7.4) across semipermeable cellulose membranes (Spectra-Por 2™, Spectrum Industries, Irvine, CA) for 6 h at 37°C. Aliquots of the post-dialysis sera and buffer were stored frozen (<—20°C) until analysis.

Drug analysis

Concentrations of cefixime in serum, urine and buffer were analyzed in duplicate by reverse-phase high-performance liquid chromatographic (HPLC) methods (Falkowski et al., 1987). The coefficient of variation of duplicate samples was always less than 11%. Cefixime is stable for at least six and three months in serum and urine, respectively, when stored frozen (Falkowski et al., 1987).

Data analysis

Pharmacokinetic parameters for cefixime were determined with model-independent methods (Gibaldi & Perrier, 1982; Pfeffer, 1984). The peak serum concentration (Cmax) and time to reach Cmax (Tmax) were determined by visual inspection of the data. The elimination rate constant (β) was determined by linear least-squares regression analysis. The elimination half-life (T1/2) was determined by the ratio of ln 2/β. The zero- and first-moment area under the curve (AUC and AUMC, respectively) values were determined by the linear trapezoidal method in the ascending and by the log trapezoidal method in the descending portions of the serum concentration vs. time profile with extrapolation to infinity. The mean residence time of the drug following an oral dose (MRTd) was determined by the ratio of AUMC/AUC. The average serum concentration (Cave) of cefixime over the dosing interval (τ = 24 h) was determined by AUC/τ. Renal clearance (CLR) of cefixime was determined from the ratio of the 24 h urinary recovery (AER24) and AUC0-24. The CLR of unbound drug was determined as the ratio of CLR/free fraction (f0) of cefixime. The percent of the drug recovered unchanged in urine (f0) was determined from AER24/Dose. The f0 of cefixime in serum was determined with classical methods (expressed as the ratio of the cefixime concentrations in the buffer/serum compartments corrected for volume shift (Bialer et al., 1986)).

Each of the pharmacokinetic parameters for cefixime was statistically analyzed (1) on each of the two days by means of intersubject ANOVA of the young and elderly data, (2) for each age by means of intrasubject ANOVA of the day one and five data, and (3) for all data utilizing a two-way ANOVA of all data (Snedecor & Cochran, 1967). Wherever the two-way ANOVA showed a non-significant interaction, the pooled data was used which allowed for a greater power for the comparison. The analysis of covariance was used to evaluate the correlation between creatinine clearance (CLR) and selected pharmacokinetic parameters. All hypotheses were tested at the P = 0.05 level of significance.

Results

Over the five day study period, no significant clinical events or changes in laboratory findings were observed in any of the young or elderly volunteers. Side effects were
generally mild gastrointestinal reactions; soft or loose stools (in 6/12 and 9/12 young and elderly subjects, respectively) which resolved within one to two days after dosing and did not require any medical treatment. All subjects were able to continue for the full period of dosing. The serum concentration time profiles in subjects with these soft or loose stools were comparable to those of subjects not reporting any side effects.

Mean serum concentrations of cefixime during the five day study are presented in Figure 2. Mean $C_{\text{max}}$ values on days one and five were lower in the young than in the elderly subjects (Table II); differences in $C_{\text{max}}$ values between age groups on these days were up to 26% (age ratio 1·25 with 95% confidence limits (C.L.) of 0·97 and 1·62), although the differences were not significant ($P > 0·05$). Day five $C_{\text{max}}$ values in both age groups were higher than day one ($P < 0·05$) (day ratio 1·19; 95% C.L. of 1·09 and 1·31), although no day or age interactions were noted. The $\text{AUC}_{0-24}$ accounted for greater than 98% of the $\text{AUC}_{0-\infty}$ for both age groups on day one. The mean $\text{AUC}_{0-\infty}$ value in the elderly on day one was higher ($P < 0·05$) than in the young (mean age ratio of 1·45; 95% C.L. of 1·1 and 1·9). Similar results were observed on day five. For both age groups, AUC values were higher on day five when compared to those on day one ($P < 0·05$) (day ratio of 1·2 with 95% C.L. of 1·1 and 1·3). Mean values for $T_{\text{max}}$, $T_{1/2}$, and $\text{MRT}_{\text{al}}$ in the elderly were also significantly greater ($P < 0·05$) than those in the young on both days one and five. Average serum concentrations ($C_{\text{av}}$) over the 24 h dosing interval in the elderly were also higher (mean ratio of 1·4, range 1·1–1·9%) than those in the young. Predose serum concentrations ($C_{\text{min}}$) on days two, three, four and five in the elderly (range 0·18–0·24 mg/l) were about two-fold greater ($P < 0·05$) than those in the young (range...
Table II. Pharmacokinetic parameters (mean ± s.d.) for cefixime in both young and elderly subjects

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Day 1 young</th>
<th>Day 1 elderly</th>
<th>Day 5 young</th>
<th>Day 5 elderly</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{max} (mg/l)</td>
<td>3.88 ± 1.30</td>
<td>4.90 ± 1.22</td>
<td>4.74 ± 1.43*</td>
<td>5.68 ± 1.83</td>
</tr>
<tr>
<td>T_{max} (h)</td>
<td>3.7 ± 0.9</td>
<td>4.2 ± 0.4</td>
<td>3.9 ± 0.3</td>
<td>4.3 ± 0.6*</td>
</tr>
<tr>
<td>AUC_{0-24} (mg · h/l)</td>
<td>28.2 ± 10.1</td>
<td>40.0 ± 10.7*</td>
<td>34.2 ± 11.9*</td>
<td>47.8 ± 18.0*</td>
</tr>
<tr>
<td>AUC_{0-∞} (mg · h/l)</td>
<td>28.6 ± 10.3</td>
<td>41.0 ± 11.2*</td>
<td>34.9 ± 12.2*</td>
<td>49.5 ± 19.1*</td>
</tr>
<tr>
<td>T_{1/2} (h)</td>
<td>3.2 ± 0.5</td>
<td>3.9 ± 0.5*</td>
<td>3.5 ± 0.6</td>
<td>4.2 ± 0.4*</td>
</tr>
<tr>
<td>MRT_{al} (h)</td>
<td>6.7 ± 1.0</td>
<td>7.9 ± 0.6*</td>
<td>6.8 ± 0.8</td>
<td>8.3 ± 0.8*</td>
</tr>
<tr>
<td>C_{rev} (mg/l)</td>
<td>1.19 ± 0.43</td>
<td>1.71 ± 0.47*</td>
<td>1.42 ± 0.50*</td>
<td>1.99 ± 0.75*</td>
</tr>
<tr>
<td>C_{min} (mg/l)</td>
<td>0.07 ± 0.06</td>
<td>0.18 ± 0.09*</td>
<td>0.09 ± 0.08</td>
<td>0.19 ± 0.09*</td>
</tr>
<tr>
<td>A_{E0-24} (mg)</td>
<td>71.6 ± 28.9</td>
<td>80.7 ± 17.8</td>
<td>80.7 ± 33.6</td>
<td>98.3 ± 30.6*</td>
</tr>
<tr>
<td>fe (%)</td>
<td>17.9 ± 7.3</td>
<td>20.2 ± 4.4</td>
<td>20.2 ± 8.4</td>
<td>24.6 ± 7.6</td>
</tr>
<tr>
<td>CI (1/h)</td>
<td>2.58 ± 0.48</td>
<td>2.04 ± 0.30*</td>
<td>2.34 ± 0.36*</td>
<td>2.10 ± 0.30</td>
</tr>
<tr>
<td>CI (unbound) (1/h)</td>
<td>7.82 ± 1.45</td>
<td>5.83 ± 0.86*</td>
<td>7.09 ± 1.09*</td>
<td>6.00 ± 0.86</td>
</tr>
<tr>
<td>f_{u} (%) 0 h</td>
<td>32 ± 4</td>
<td>34 ± 5</td>
<td>33 ± 5</td>
<td>37 ± 6</td>
</tr>
<tr>
<td>4 h</td>
<td>32 ± 2</td>
<td>34 ± 2</td>
<td>30 ± 2</td>
<td>33 ± 3</td>
</tr>
<tr>
<td>12 h</td>
<td>34 ± 7</td>
<td>36 ± 2</td>
<td>33 ± 7</td>
<td>37 ± 3</td>
</tr>
</tbody>
</table>

* Difference between days was significant (P < 0.05).
* Difference between age groups was significant (P < 0.05).
* Significant age × day interaction.

0.09—0.11 mg/l). A significant (P < 0.05) age and day interaction was observed for the C_{min} values.

Urine drug concentrations at each of these collection times are presented in Figure 3. Although day-to-day variation in urinary recovery was significant (Table II), differences between days 1 and 5 were not manifestations of any systematic trend.

The f_{u} of cefixime in serum samples obtained before (0 h) and after the dose (4 and 12 h) are presented in Table II. No volume shift correction was necessary for any of the f_{u} values. The mean f_{u} values in the young were unchanged over the 12 h period following the initial dose, averaging approximately 33% and no differences were observed in the binding of cefixime after oral dosing for five days. The f_{u} values in the elderly were comparable to those in the young (P > 0.05).

The CI of cefixime in the young on day one was significantly greater (about 20%) than in the elderly (P < 0.05). A significant linear correlation (P < 0.05) was observed between the CI for both total and unbound drug and creatinine clearance (Cl_{cr}) for the two age groups. No significant (P > 0.05) association was found between Cl_{cr} and either AUC, MRT, A_{E0-24} or T_{1/2}.

Discussion

There were somewhat larger (up to 20%) C_{max} and AUC values observed for cefixime on day five (relative to day one) for both age groups in this study. In contrast, results from a previous study showed no significant changes in serum concentrations or urinary recovery in young adults over a 15-day dosing period. In that study, although serum concentrations were also somewhat higher (about 20%) on day eight (versus day 1), they were back to day one values after 15 days of dosing (Faulkner et al., 1987). Therefore, the somewhat higher serum concentrations on day five in this study may represent day to day variability and the differences may not have clinical
Figure 3. Mean urine concentrations of cefixime at 0-2 (■), 2-4 (■), 4-6 (□), 6-8 (□), 8-12 (□) and 12-24 h (■) after 400 mg single daily doses on days 1 and 5 in young and elderly subjects. Bars show 1 sd from mean.

significance. The mean difference in drug $T_{1/2}$ between the elderly and young on days one and five (~ 0-7 h) may also not be clinically significant. The protein binding of the drug was similar in both age groups (about 33% bound) and the values of $f_u$ observed are consistent with those previously reported from in-vitro studies in serum obtained from young subjects (Bialer et al., 1986). A previous study showed that the $f_u$ of cefixime in man is concentration independent at concentrations to at least 30 mg/l (Bialer et al., 1986).

The $Cl_i$ of total and unbound cefixime was highly correlated with renal function as assessed by $Cl_{cr}$ in both the elderly and young. The $Cl_i$ of cefixime adjusted for unbound drug ($f_u$), over days one and five, was approximately 125–135 ml/min in the young and 99–101 ml/min in the elderly; values which are comparable to the respective mean $Cl_{cr}$ values for each age group. Since the $Cl_i$ of cefixime approximates the glomerular filtration rate, the $Cl_i$ values for cefixime based on free drug determined in this study suggest that the net renal excretion of cefixime is predominately via glomerular filtration in man. Alternatively, if secretion and reabsorption do occur, their contributions are apparently offset by one another. The pharmacokinetic results obtained in the young and elderly are consistent with those previously reported (Guay et al., 1986), where the $Cl_i$ of total cefixime was also correlated with $Cl_{cr}$. In that study,
the pharmacokinetics of cefixime were changed from that in healthy adults only in patients with severe reductions in renal function, where $Cl_a$ values were less than 20 ml/min/1.73 m$^2$.

The small differences in the serum concentrations and pharmacokinetic profile of cefixime between the elderly and young cannot be entirely explained by differences in the $Cl_i$ and urinary excretion of the drug, since the protein binding of cefixime in elderly subjects was comparable to that in the young. Therefore, the somewhat higher serum concentrations and urinary recovery of drug observed in the elderly may be a result of a multitude of small differences, including differences in $Cl_i$, absolute bioavailability, rate of absorption, excretion into bile, prolonged enterohepatic recycling and/or tissue distribution of the drug. This contention is supported, in part, by the longer MRT$_{al}$ and $T_{max}$ values observed in the elderly.

It was previously observed that serum concentrations of cefixime in patients with significant renal impairment can be increased by as much as two- to three-fold relative to those in subjects with normal renal function (Guay et al., 1986). Although no toxicity was seen even at these higher serum concentrations, dosage adjustment is recommended in patients with significantly impaired renal function where $Cl_a$ is less than 20 ml/min/1.73 m$^2$, where the $Cl_i$ of cefixime is significantly reduced ($\geq$ 50% decrease) and the biologic $T_{1/2}$ prolonged (\sim 11 h) (Guay et al., 1986). Therefore, since cefixime shows a wide spectrum of safety in the elderly and young and the magnitude of the differences observed for many of the pharmacokinetic parameters between elderly and young subjects are not of clinical significance, a dosage adjustment in the elderly is not necessary.

References


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