Pharmacokinetics of Cefmetazole in Elderly Patients and Healthy Volunteers

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The pharmacokinetics of cefmetazole were investigated in 7 elderly patients (4 males, 3 females) and in 5 healthy volunteers (males). The drug was given intravenously at 10 mg/kg. The creatinine clearance values of the elderly patients and healthy volunteers were 53.6 to 64.5 ml/min and 93.7 ml/min, respectively. The concentrations of cefmetazole in the serum and urine were determined by bioassay, and pharmacokinetic parameters were calculated on the basis of a two-compartment open model. The cumulative urinary excretion of cefmetazole at 8 hr after its injection was about 90% of the total dose in healthy volunteers, and about 60% of the dose in elderly patients. A negative correlation between age and the elimination rate constant ($\beta$), and a positive correlation between age and the volume of distribution were observed. From these results, it was suggested that the decreased renal function reduced urinary excretion of cefmetazole in elderly patients, while the increased volume of distribution of cefmetazole, in particular, in bedridden elderly patients may be caused by age.

Key words: cefmetazole, pharmacokinetics, elderly patients, renal function, volume of distribution
Introduction

Cefmetazole (7 \(\beta\)-substituted-thioacetamide 7 \(\alpha\)-methoxy-cephalosporines) is a cephemycin C analog that has been shown to have not only potent broad-spectrum antibacterial activity but also remarkable stability against \(\beta\)-lactamase\(^1\). Elderly patients often suffer from urinary tract infection and complications from this may cause high fever. Antibiotics with broad-spectrum bacteriocidal activity are widely used in the treatment of such complications. In general, renal function, especially creatinine clearance, decreases with age. Cefmetazole is mainly excreted unchanged in the urine. In this study, we compared the pharmacokinetics of cefmetazole in elderly patients and healthy young volunteers.

Methods

Subjects

The pharmacokinetics of cefmetazole were studied in 7 elderly patients: 3 bedridden female patients, 84.3±6.4 years of age (mean ± S. D.), with an average body weight of 32.8±5.3 kg and creatinine clearance value of 53.6±3.9 ml/min, and 4 physically normal male patients (65.5±0.6 years old, 52.1±2.3 kg body weight, 64.5±10.4 ml/min creatinine clearance). Five healthy male volunteers were also examined (26.6±5.3 years old, 60.7±5.7 kg body weight, 93.7±8.6 ml/min creatinine clearance). In both elderly patients and healthy volunteers, clinical history review, physical examination, chest X-ray, and blood and urine analyses were performed before drug administration and were found to be within or near the normal ranges. In particular, the liver function test in these patients and the healthy volunteers were within the normal ranges. Creatinine clearance was estimated from the serum creatinine level and age by the method of Jelliffe\(^2\). Elderly patients and healthy volunteers participated in this study after informed consent was obtained.

Drug administration and drug assay

The subjects were given an intravenous injection of cefmetazole (CS-1170, CMZ; Sankyo Co., Ltd., Tokyo Japan) at a dose 10 mg/kg body weight. Blood samples were collected at 5, 15, 30 min, 1, 2, 4 and 6 hr after the injection and urine samples were collected at 0-2, 2-4, 4-6 and 6-8 hr after the injection. These samples were stored at -20°C until assayed. The concentrations of cefmetazole in the serum and urine were determined by the thin layer cup-plate method, with Micrococcus luteus ATCC 9341 as the test organism and heart infusion agar as medium. For measurement of serum concentrations, a series of standard solution in pooled normal human serum was prepared. The assay range was from 200 to 0.78 \(\mu\)g/ml. For measurement of urinary concentrations, a series of standard solutions of 20 to 1.25 \(\mu\)g/ml in 1% phosphate buffer (pH 6.0) was prepared. Urine was diluted with 1% phosphate buffer (pH 6.0) to give solutions containing about 5 \(\mu\)g/ml of CMZ.

Pharmacokinetic parameters were calculated according to a two-compartment open model\(^3\) using the non-linear regression program Nonline\(^4\) on an IBM 4341 computer.

Results

The serum concentrations of cefmetazole in elderly bedridden patients, elderly ambulatory patients, and healthy volunteers after intravenous injection of 10 mg/kg are shown in Fig. 1. In each group, the mean serum concentration of cefmetazole decreased rapidly in the first 15 to 30 min (\(\alpha\) distribution phase). The subsequent decrease of the serum concentration was slower in elderly patients than in healthy volunteers (\(\beta\) elimina-
The pharmacokinetic parameters in elderly patients and healthy volunteers are shown in Tab. 1. The creatinine clearance (Clcr) values in elderly bedridden patients, elderly patients and healthy volunteers were 53.6, 64.5, and 93.7 ml/min, respectively, the values in the former groups being significantly lower than that in healthy volunteers. The values of the elimination rate constant (β) were 0.4 and 0.5 hr⁻¹, and of the half-life (t1/2β) were 1.8 and 1.3 hr, in the bedridden and ambulatory elderly patients, respectively, which were significantly lower in the former value and higher in the latter than the values of 0.7 hr⁻¹ and 1.0 hr, respectively, in healthy volunteers. The apparent volume of distribution in the steady state (Vdss) in elderly bedridden patients was 0.35 l/kg, which was significantly higher than the value of 0.24 l/kg in healthy volunteers. The elimination rate constants (k12, k21, kel), the apparent volumes of distribution in the central (V1), and peripheral (V2) compartments and AUC in elderly bedridden patients were not significantly different from those in healthy volunteers.

The cumulative urinary excretion curves in elderly patients and healthy volunteers are shown in Fig. 2. Cumulative urinary excretion of cefmetazole in healthy volunteers after 2 hr (about 70% of the total dose) was significantly higher than the values in both groups of elderly patients (30 to 40%), but the curves between elderly bedridden-

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Elderly bedridden patients</th>
<th>Elderly ambulatory patients</th>
<th>Healthy volunteers</th>
</tr>
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<tbody>
<tr>
<td>n</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Clcr (ml/min)</td>
<td>53.6±3.9***</td>
<td>64.5±10.4**</td>
<td>93.7±8.6</td>
</tr>
<tr>
<td>a (hr⁻¹)</td>
<td>16.1±7.9</td>
<td>6.7±2.2</td>
<td>8.1±2.9</td>
</tr>
<tr>
<td>β (hr⁻¹)</td>
<td>0.4±0.1*</td>
<td>0.5±0.1*</td>
<td>0.7±0.1</td>
</tr>
<tr>
<td>t1/2β (hr)</td>
<td>1.8±0.7*</td>
<td>1.3±0.2*</td>
<td>1.0±0.2</td>
</tr>
<tr>
<td>k12 (hr⁻¹)</td>
<td>9.9±8.3</td>
<td>2.7±0.8</td>
<td>3.9±2.1</td>
</tr>
<tr>
<td>k21 (hr⁻¹)</td>
<td>5.2±3.2</td>
<td>3.5±1.5</td>
<td>3.1±1.0</td>
</tr>
<tr>
<td>kel (hr⁻¹)</td>
<td>1.4±0.7</td>
<td>1.1±0.1**</td>
<td>1.9±0.2</td>
</tr>
<tr>
<td>V1 (l/kg)</td>
<td>0.13±0.07</td>
<td>0.15±0.03*</td>
<td>0.11±0.02</td>
</tr>
<tr>
<td>V2 (l/kg)</td>
<td>0.22±0.11</td>
<td>0.12±0.01</td>
<td>0.13±0.03</td>
</tr>
<tr>
<td>Vdss (l/kg)</td>
<td>0.35±0.05***</td>
<td>0.27±0.04</td>
<td>0.24±0.03</td>
</tr>
<tr>
<td>AUC0→∞ (µg/·hr)</td>
<td>73.4±20.0</td>
<td>69.5±14.2</td>
<td>55.0±7.5</td>
</tr>
</tbody>
</table>

Significance of difference from healthy volunteers (t test): * P<0.05, ** P<0.01, *** P<0.001. These pharmacokinetic parameters were calculated by using the methods described in the paper.

a : distribution rate constant, β : elimination rate constant
k12 : distribution rate constant from central to peripheral compartment
k21 : distribution rate constant from peripheral to central compartment
kel : elimination rate constant from central compartment to outside
V1 : apparent volume of distribution in central compartment
V2 : apparent volume of distribution in peripheral compartment
t1/2β : half-life in elimination phase
Vdss : apparent volume of distribution in steady state
den patients and elderly patients were not significantly different. The cumulative urinary excretion in healthy volunteers after 8 hr (about 90%) was still higher than those in elderly patients (60 to 65%).

As shown in Fig. 3, a positive correlation was found between $\beta$ and Clcr in all subjects: $Y = 0.0053X + 0.1897$ ($r = 0.6652$, $P < 0.02$). A negative correlation was found between $\beta$ and age in all subjects as shown in Fig. 4: $Y = -0.0050X + 0.8555$ ($r = -0.8177$, $P < 0.005$). Thus the decrease in the elimination rate constant with age was caused by decrease in Clcr in elderly patients.

The positive correlation found between the Vdss and age in all subjects is shown in Fig. 5, $Y = 0.0017X + 0.1814$ ($r = 0.7645$, $P < 0.005$).

From these results, the decreased $\beta$ and increased Vdss of cefmetazole in elderly patients...
Fig. 2 Cumulative urinary excretions of cefmetazole after its injection at 10 mg/kg into bedridden elderly patients (—△—), elderly patients (— ● —) and healthy volunteers (— ○ —). Cumulative urinary excretions are shown as percentages of the dose (10 mg/kg) and values are means±S.D.

Discussion

Elderly bedridden patients often suffer from urinary tract infection and cefmetazole is commonly used for therapy of the infection, because it has broad-spectrum antibacterial activity and remarkable stability against β-lactamase. It is generally accepted that renal function, especially creatinine clearance, decreases in elderly patients, and when cefmetazole is used for these patients, renal function should be considered in determining the dosage schedule because this drug is excreted mainly unchanged in the urine.

In this study, we compared the pharmacokinetics of cefmetazole in elderly patients and healthy...
Fig. 3  Correlation between the elimination rate constant ($\beta$) and creatinine clearance. $Y = 0.0053X + 0.1897$ and $r = 0.6652$ ($P < 0.02$). Bedridden elderly patients ($\Delta$), elderly patients ($\bullet$), healthy volunteers ($\bigcirc$).

Fig. 4  Correlation between elimination rate constant ($\beta$) and age. $Y = -0.0050X + 0.8555$ and $r = -0.8177$ ($P < 0.005$). Symbols are as for Fig. 3.
volunteers. As shown in Tab. 1, the creatinine clearances in elderly bedridden patients and elderly ambulatory patients were significantly less than in healthy volunteers. Fig. 3 shows a significant positive correlation between $\beta$ and the creatinine clearance in all subjects in this study. Ohkawa et al.\textsuperscript{5} studied the pharmacokinetics of cefmetazole in patients with impaired renal function, finding that the elimination rate constant decreased, while $t_{1/2}$ and AUC increased with decrease in creatinine clearance, and that there was good correlation between these pharmacokinetic parameters and the creatinine clearance. Their results with elderly patients were similar to ours, but they gave cefmetazole to patients by intravenous drip and calculated pharmacokinetic parameters on the basis of a one-compartment model. Fig. 4 shows decreased $\beta$ with age, which was found to result from age-dependent decrease of renal function in elderly patients. The increased $T_{1/2}$ and AUC in elderly patients may also be related to this decrease in $\beta$. The results in cumulative urinary excretion of cefmetazole (Fig. 2) showed that the excretions in elderly patients were about two-thirds of that in healthy volunteers, even at 8 hr after cefmetazole administration, and that there was no significant difference between the excretions in bedridden and ambulatory elderly patients. The decreased cumulative urinary excretion of cefmetazole in elderly patients is similar to the cases of amikacin and cephalothin, which are excreted mainly unchanged in the urine\textsuperscript{6}. The $V_{ds}$ in elderly patients, especially elderly bedridden patients, was significantly higher than in healthy volunteers, but no consistent relationship was demonstrated between $V_d$ and creatinine clearance in patients with renal impairment\textsuperscript{6}. The $V_d$ of diazepam increases with age without alteration of drug clearance\textsuperscript{7}. In general, serum albumin levels decrease gradually with age\textsuperscript{8}. We have reported that the apparent $V_d$ of tenoxicam, a thieno-

![Graph](image)

**Fig. 5** Correlation between $V_{ds}$ and age. $Y = 0.0017X + 0.1814$ and $r = 0.7645 \quad (P < 0.005)$. Symbols are as for Fig. 3.
thiazine derivative with analgesic and anti-inflammatory properties, in bedridden elderly female patients was significantly larger than in healthy volunteers\(^9\). With warfarin and phenytoin, good correlations were found between reduction in protein binding and reduction in plasma albumin concentration in elderly patients\(^10\)\(^11\). Craig et al.\(^{12}\) found that the \(V_d\) of cefazolin increased with decrease in renal function and explained their results on the basis of change in protein binding. In contrast, the apparent \(V_d\) of cefamandole decreased with decrease in creatinine clearance in patients with renal impairment, while the serum albumin levels in these patients were not different from those of healthy volunteers\(^13\). In the case of cefmetazole, it seems that the increase of \(V_d\) in bedridden elderly patients may be related to the decrease in the serum albumin level and also to reduced cardiac output\(^4\) and slower peripheral circulation\(^5\) and to increased extracellular fluid; however, which of the factors may be related to the increase of \(V_d\) in these patients could not be determined in the present study. In addition to these factors, the differences in physical activity, age and sex between these bedridden and ambulatory elderly patients may be related to the increase of \(V_d\) in bedridden elderly patients.

From these results, the decreased urinary excretion of cefmetazole in elderly patients is concluded to be affected by the decrease in renal function with age, and we are now investigating which factors may effect the increase of \(V_d\) in elderly patients. In any case, it is clear that when cefmetazole is given to elderly patients, especially bedridden elderly patients, increased \(t_{1/2}\) and \(V_{ds}\) must be considered in determining a suitable dose that does not cause intoxication.

### References

12. Craig, W. A., Welling, P. G., Jackson, T. C. et al. : Pharmacology of cefazolin and other cephalosporins in patients with renal insuffi-
