Pharmacokinetics of Carumonam in Patients with Renal Insufficiency

FRITZ HORBER,1 HERMANN-JOSEF EGGER,2 ERHARD WEIDEKAMM,2 URS C. DUBACH,3 FELIX J. FREY,1 PETER J. PROBST,4 AND KLAUS STOECKEL2*

Pharmaceutical Research Department2 and Department of Clinical Research,2 F. Hoffmann-La Roche & Co., Ltd., and Therapeutic Investigation Station, University Medical Outpatient Department, Cantonal Hospital,3 CH-4002 Basel, and University Medical Outpatient Department, Inselspital, CH-3010 Bern,1 Switzerland

Received 6 May 1985/Accepted 4 October 1985

The pharmacokinetics of carumonam after a single 1,000-mg intravenous infusion (20 min) were evaluated in four groups of subjects who had various degrees of renal impairment: group 1, CLCR > 60 ml/min; group 2, CLCR = 30 to 60 ml/min; group 3, CLCR = 10 to 30 ml/min; and group 4, CLCR < 10 ml/min). The elimination half-life of carumonam increased with decreasing creatinine clearance (CLCR) from 1.7 h in group 1 to 11.3 h in group 4. Peak carumonam concentration (103 μg/ml) and steady-state volume of distribution (12.8 liters) did not change with decreasing CLCR. Total body clearance (r = 0.98), renal clearance (r = 0.98), and nonrenal clearance (r = 0.67) of carumonam correlated with decreasing CLCR. Mean nonrenal clearance was 21 ml/min in group 1 and 12 ml/min in group 4. With regard to dosage, patients with a CLCR above 60 ml/min should receive their standard maintenance dose of carumonam without any changes; patients with a CLCR between 30 and 60 ml/min should receive the dose every 12 h; and individuals with a CLCR between 10 and 30 ml/min should be given the dose once a day. Patients with a CLCR of less than 10 ml/min should receive one-half of the dose once a day. Our recommended dosage regimens should produce within the CLCR borderlines of each group average plasma concentrations that are between one and two times that achieved in normal subjects with a t.i.d. dosage regimen.

Carumonam (Fig. 1) is a new synthetic N-sulfonated monocyclic beta-lactam antibiotic. This compound is highly stable against both chromosomal- and plasmid-mediated beta-lactamases and has broad-spectrum activities against gram-negative bacteria. In vivo and in vitro activities of carumonam are comparable to those of aztreonam, a structurally related compound (9). The pharmacokinetic characteristics of carumonam include low protein binding (fubound = 0.82); elimination primarily by glomerular filtration (furextracellular water space; and a half-life of elimination (t1/2) between 1.4 and 2.3 h (20). These pharmacokinetic characteristics are similar to those of the cephalosporins cefaludin, ceftizoxime, and ceftazidime (15). As with these and other beta-lactam antibiotics with low protein binding and high urinary recovery, loss of renal function should result in an almost proportional decrease in body clearance and a corresponding increase in biological half-life for carumonam.

The purpose of this study was to define the pharmacokinetic behavior of carumonam in patients with renal insufficiency and to deduce from these data appropriate dosage schedules for such patients.

MATERIALS AND METHODS

Subjects. All healthy volunteers and renal disease patients gave informed written consent before entering the study. The study protocols were approved by the Institutional Committees of Human Investigations, Medical Outpatient Department, University of Bern (renal disease patients), and the Department of Internal Medicine, Medical Outpatient Department, Cantonal Hospital, Basel (healthy volunteers). In total, the elimination kinetics of carumonam were studied in 8 healthy volunteers (7 men and 1 woman) and 17 patients (11 men and 6 women) with different degrees of renal function. The subjects were categorized according to creatinine clearance (CLCR): group 1, subjects with normal and close-to-normal renal function (CLCR > 60 ml/min); group 2, patients with mild renal insufficiency (CLCR of 30 to 60 ml/min); group 3, patients with moderate renal insufficiency (CLCR of 10 to 30 ml/min); and group 4, patients with severe renal insufficiency (CLCR < 10 ml/min). The characteristics of the four groups are shown in Table 1. The normal volunteers (most of the subjects in group 1) ranged in age from 20 to 26 years (mean, 23 ± 2 years) and had heights of 170 to 195 cm (mean, 187 ± 9 cm), weights of 55 to 84 kg (mean, 69 ± 9 kg), surface areas of 1.65 to 2.16 m² (6) (mean, 1.86 ± 0.16 m²), and CLCR of 82 to 120 ml/min (mean, 99 ± 15 ml/min). Before enrollment and after completion of the study, each subject received a complete physical examination, a 12-lead electrocardiogram, and a series of laboratory tests (hematology, blood chemistry, urinalysis). In healthy volunteers the CLCR was the average of two values that were calculated from serum creatinine concentrations (3). CLCR in renal disease patients was calculated as the average of two separate measurements based on 24-h urine collections. Excluded from the study were individuals with hepatic dysfunction as determined by elevated alanine aminotransferase, aspartate aminotransferase, γ-glutamyl transferase, and bilirubin values and individuals with a known history of drug allergy. The patients received no other drugs with antibacterial activity during 2 weeks before and while participating in this study.

Drug administration and sample collection. Carumonam was administered as a solution of the lyophilized disodium salt. The equivalent of 1.020 mg (healthy volunteers) or 1.040 mg (renal disease patients) of carumonam (free acid) was dissolved in 20 ml of sterile water and infused into a forearm vein with a Harvard syringe infusion pump. The duration of infusion was 20 min.

In addition to the blank samples (10 ml), 5-ml blood samples were obtained from an indwelling catheter into citric acid-containing VACUTAINERs (Becton Dickinson

* Corresponding author.
Vacutainer Systems, Rutherford, N.J.) 5, 10, and 15 min after the start and exactly at the end of the drug infusion (C\text{max}). Further samples were collected at frequent intervals after the end of infusion: up to 12 h in healthy volunteers; up to 28 h in renal disease patients with a CL\text{CR} > 15 ml/min; and up to 49 h in patients with a CL\text{CR} < 15 ml/min. Within 30 min of collection each blood sample was centrifuged at 1,000 x g for 15 min, and the plasma was carefully transferred to glass tubes and stored at -20°C. Urine specimens were collected from subjects with a CL\text{CR} of more than 15 ml/min at the following time intervals: -12 to 0, 0 to 2, 2 to 4, 4 to 6, 6 to 8, 8 to 10, 10 to 12, 12 to 24 h. For patients with a CL\text{CR} of less than 15 ml/min, the urine collection intervals were: -24 to 0, 0 to 12, 12 to 24, 24 to 48 h. The pH of all urine samples was measured. Specimens with pH values above 6.5 were titrated to pH 6 with citric acid crystals. All urine samples were frozen at -20°C until assayed.

**Assay procedures.** A high-pressure liquid chromatographic method, described in detail elsewhere (H.-J. Egger and G. Fischer, submitted for publication), was used to determine plasma and urine levels of carumonam.

Briefly, the sample work-up involved buffering the plasma samples to pH 6.0 with potassium phosphate buffer, protein precipitation with acetonitrile, and purification of the aqueous phase containing the beta-lactam by extraction with methylene chloride. Urine was simply diluted with buffer.

The separation and quantification were achieved by using a mobile phase based on either ion suppression or ion-pair chromatography on a reversed-phase column with UV detection. For the analysis of plasma samples from patients with renal disease, a different mobile phase with precolumn backflash was applied. The limit of determination with 0.5-ml plasma specimens was 0.5 and 2 
\mu g/ml for samples from healthy volunteers and patients suffering from severe renal disease, respectively; for urine samples, the limit was 25 and 20 \mu g/ml, respectively, with 50-\mu l specimens.

The assay was linear in the range of 0.5 to 200 \mu g/ml of plasma and 20 to 8,000 \mu g/ml of urine. The coefficient of variation (r^2) was 0.9999 (0.999 for determination of plasma from patients with renal disease), using the weighting factor 1/x^2. The recovery of Ro 17-2301 was quantitative. The interassay variation during this study was less than 7% (0.5 to 80 \mu g/ml) for plasma and less than 6% (25 to 4,000 \mu g/ml) for urine.

**Pharmacokinetic analysis.** With the exception of one subject, a biexponential equation was fitted as reported previously (20) to the carumonam plasma concentration-time data (C\text{t}), using the NONLIN (12) computer program. In one case visual inspection showed that a monoequational equation described the C\text{t} data adequately. Area under the plasma concentration-time curve (AUC\text{0-\infty}), total body clearance (CL\text{B}), renal clearance (CL\text{R}), and volume of distribution at steady state (V\text{SS}) with reference to total (bound plus unbound) drug were calculated as previously described (20). Nonrenal clearance (CL\text{N}) with reference to total drug was determined by CL\text{B} = CL\text{R}.

**Statistical analysis.** Simple linear correlations were examined between CL\text{B}, CL\text{R}, and CL\text{CR}. The rank correlation coefficient of Spearman was used to test for linear correlations between CL\text{R}, V\text{SS}, C\text{max}, and CL\text{CR}. A one-way analysis of variance was used to examine between-group differences (Table 2). Differences between the healthy volunteers of this and a former study (20) in the values for V\text{SS}, CL\text{B}, CL\text{R}, and AUC\text{0-\infty} were examined by the two-tailed Student’s t test.

## RESULTS

The biochemical parameters characterizing liver function (alanine aminotransferase, aspartate aminotransferase, \gamma-glutamyl transferase, alkaline phosphatase, albumin, and bilirubin concentrations) were within the normal range in all subjects (Table 1). The concentrations of carumonam in plasma declined in all but one of the subjects in a biexponential fashion (see Pharmacokinetic analysis) (Fig. 2). The mean maximum (± standard deviation [SD]) plasma concentrations (C\text{max,1}) measured at the end of the 20-min infusion were similar for groups 1 to 4: 99.2 ± 16.5, 107.4 ± 11.9, 108.2 ± 19.6, and 102.5 ± 22.7 \mu g/ml, respectively. The rate of decline of the carumonam plasma concentrations during the postdistributive phase decreased, however, with decreasing renal function. For example, the average (± SD)

<table>
<thead>
<tr>
<th>Group</th>
<th>n (male/ female)</th>
<th>Age (yr)</th>
<th>Ht (cm)</th>
<th>Wt (kg)</th>
<th>Surface area (m²)</th>
<th>Serum vol (mmol/liter)</th>
<th>Serum creatinine (μmol/liter)</th>
<th>CL\text{R} (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8/1</td>
<td>26 ± 9 (20–49)</td>
<td>177 ± 9 (170–195)</td>
<td>69 ± 8 (55–84)</td>
<td>1.86 ± 0.15 (1.65–2.16)</td>
<td>5.2 ± 1 (3.9–6.3)</td>
<td>104 ± 17 (84–143)</td>
<td>95 ± 18 (67–120)</td>
</tr>
<tr>
<td>2</td>
<td>3/1</td>
<td>52 ± 13 (36–65)</td>
<td>165 ± 3 (160–168)</td>
<td>64 ± 9 (53–73)</td>
<td>1.70 ± 0.12 (1.54–1.82)</td>
<td>13.4 ± 4 (9–17)</td>
<td>266 ± 142 (134–459)</td>
<td>36 ± 6 (31–44)</td>
</tr>
<tr>
<td>3</td>
<td>3/2</td>
<td>65 ± 8 (54–75)</td>
<td>164 ± 5 (165–169)</td>
<td>68 ± 11 (51–80)</td>
<td>1.74 ± 0.16 (1.49–1.91)</td>
<td>20.6 ± 4 (14–25)</td>
<td>315 ± 114 (182–463)</td>
<td>18 ± 6 (12–27)</td>
</tr>
<tr>
<td>4</td>
<td>4/3</td>
<td>49 ± 13 (23–64)</td>
<td>166 ± 14 (150–193)</td>
<td>61 ± 12 (47–80)</td>
<td>1.67 ± 0.20 (1.45–2.01)</td>
<td>28.3 ± 9 (21–47)</td>
<td>774 ± 154 (524–920)</td>
<td>3.4 ± 3.9 (0–8.2)</td>
</tr>
</tbody>
</table>

* Data are x ± SD (range).
plasma concentration at 9 h after the end of infusion was 1.8 ± 1.5 μg/ml in group 1 compared with 44.9 ± 8 μg/ml in patients with a CLCR of less than 10 ml/min (group 4).

With declining renal function, there were marked increases in AUC₀-∞ and t₁/₂δ, decreases in CL₄, CL₄, and urinary recovery, and a slight but significant decrease in CL₁₉R (Table 2). The magnitude of V₃₃ was not related to CLCR.

The mean (± SD [range]) kinetic parameters of the eight healthy volunteers were: AUC₀-∞, 167.4 ± 23.4 (131.8 to 214.1) μg • h/ml; t₁/₂δ, 1.6 ± 0.1 (1.4 to 1.7) h; CL₄, 103.3 ± 14 (79.4 to 129) ml/min; CL₁₉R, 81.7 ± 12 (68.8 to 106.9) ml/min; Cl₁₉R, 21.6 ± 5.3 (10.6 to 28.9) ml/min; urinary recovery, 79.2 ± 4.7 (70.5 to 86.7)%.

**DISCUSSION**

Loss of renal function does not necessarily result in a decreased CL₄ and an increased biological half-life for renally eliminated drugs. Acidic drugs such as ceftriaxone and cefoperazone with extensive protein binding (>90%) and substantial nonrenal elimination (>30%) showed in functionally anephric patients only minor deviations from normal in their CL₄ and half-life values (1, 16). For these substances, the loss of renal function was accompanied by an increase in the free fraction in plasma, which increased their CL₁₉R for total drug (16). Although decreased protein binding of acidic drugs in renal disease patients is a general phenomenon (14, 17), marked effects on CL₄ (less so on volume of distribution) can only be expected with extensively protein-bound drugs (>90%) (17). For poorly bound drugs, the loss of renal function usually results in proportional changes in CL₄ and a corresponding prolongation of the t₁/₂δ (4, 17). The CL₁₉R and volume of distribution are under these circumstances thought to be unaffected by renal disease (4, 17). The magnitudes of the clearance and half-life changes depend only on the fraction of dose excreted in the urine of normal subjects. The larger this fraction the larger are the changes in CL₄ and t₁/₂δ (4).

Since the protein binding of carumonam is low (18% [20]) and the percentage excreted via the kidneys is high (70 to 90% [20]), a substantial decrease in CL₄ and prolongation of t₁/₂δ but no changes in V₃₃ and CL₁₉R are anticipated for carumonam in patients with decreasing renal function. The values listed in Table 2 for CL₄, t₁/₂δ, and V₃₃ and the correlation found between CL₄, CL₁₉R, and CL₁₉R (Fig. 3 and 4) are in agreement with these expectations.

The decrease in CL₁₉R with declining renal function (Fig. 2).
FIG. 3. Relationship between $CL_{i}$ of carumonam and $CL_{CR}$ in 8 healthy normal subjects (○) and 17 renal disease patients (△).

5) cannot be explained solely by the lower mean age of the subjects in group 1 since the decrease was also significant ($P < 0.05$) between groups 2 and 4. Other mechanisms responsible for the decline in $CL_{KR}$ of carumonam have not been elucidated. A similar decline in the nonrenal (mainly hepatic) clearance of other drugs has previously been reported in patients with renal failure (5, 7, 8, 19). That certain drug-metabolizing activities are decreased in acute or chronic renal failure is well established (10, 11, 13). In four of our patients (two in group 2 and one each in groups 3 and 4), function was assessed by measuring the galactose elimination capacity (data not shown) (18). Despite the absence of biochemical or anamnestic evidence of liver disease, all four patients exhibited a decreased galactose elimination capacity, indicating an impaired liver function (18).

Normally, when the relationship between $CL_{i}$ and $CL_{CR}$ is examined by linear regression (Fig. 3), it is assumed that the ordinate intercept is an estimate of $CL_{KR}$. However, since $CL_{KR}$ decreased with $CL_{CR}$ in our subjects (Fig. 5), the ordinate intercept in Fig. 3 was lower than the $CL_{KR}$ value observed in group 1. Despite the decline in $CL_{KR}$, there was a strong linear correlation ($r = 0.98$) between $CL_{i}$ and $CL_{CR}$ (Fig. 3). For practical purposes this correlation is useful, for example, in the design of carumonam dosing regimens. The parameter values reported for $V_{SS}$, $CL_{i}$, and $CL_{i}$ in normal subjects (see Results) are slightly lower than those previously reported (20). The differences are, however, insufficient to alter the previous interpretations (20). While a biological rather than a high-pressure liquid chromatographic assay was used in the previous study, identical results are obtained with both methods. The higher parameter values reported before are more likely due to a slight degradation of carumonam in the freshly drawn blood, before the plasma was separated and titrated with phosphate buffer to pH 6 for drug stabilization. It was recently discovered that freshly drawn citrated blood increases in pH to above 7.5, where carumonam is unstable (Egger and Fischer, submitted). That slight degradation artifically lowered the plasma concentrations in the previous study is also supported by the fact that the $AUC_{0-\infty}$ values for normal subjects reported here (see Results) are significantly higher ($167 \pm 23 \mu g \cdot h/ml$ versus $113 \pm 9 \mu g \cdot h/ml$ (20)). Degradation of carumonam was avoided in the present study by blood collection directly into citric acid-containing VACUTAINERs which adjusted the blood immediately to pH 6.5.

Since carumonam pharmacokinetics depend on renal function, multiple dosing regimens should be adjusted when treating patients with reduced renal function. If the same peak ($CP_{\text{max}}$), trough ($CP_{\text{min}}$), and average ($CP_{\text{avg}}$) carumonam plasma concentrations as in uncompromised patients are to be achieved, the dosing interval ($\tau$) should be increased to compensate for the decrease in $CL_{i}$ (2). To avoid long durations of subtherapeutic plasma concentrations of carumonam, however, we recommend that $\tau$ should not exceed 24 h. Instead, $\tau$ should remain at 24 h, and the dose should be decreased in patients with severe renal impairment. Based on the correlation found between carumonam $CL_{i}$ and $CL_{CR}$ ($CL_{i} = 0.939 \times CL_{CR} + 8.6$; Fig. 3) and the common relationships between dosing interval or dose and clearance (2), precise individual dosage regimens for carumonam can be designed. When the dose is kept constant the dosing interval ($\tau_{\text{ren}}$) should be:

$$\tau_{\text{ren}} = \frac{103}{0.939 \times CL_{CR} + 8.6}$$

where $\tau_{\text{norm}}$ is the dosing interval and 103 is the mean $CL_{i}$ in normal subjects (see Results). In the event that dose rather
than $\tau$ is changed the following equation can be used:

$$D_{ren} = D_{norm} \left( \frac{0.939 \times CL_{CR} + 8.6}{103} \right)$$

where $D_{ren}$ and $D_{norm}$ are the doses in renal-impaired and normal subjects, respectively. Since the beta-lactam antibiotics, including the monobactams, are relatively safe over a wide range of plasma concentrations, it is also possible to adjust the dosage intervals only over relatively widely spaced $CL_{CR}$ intervals.

For a standard dosage regimen of 0.5 to 2 g of carumonam every 8 h in normal subjects, we recommend changing $\tau$ values as follows. Patients with a $CL_{CR}$ above 60 ml/min should receive their standard maintenance dose of carumonam without any changes; patients with a $CL_{CR}$ between 30 and 60 ml/min should receive the dose every 12 h; and individuals with a $CL_{CR}$ between 10 and 30 ml/min should be given the dose once a day. Patients with a $CL_{CR}$ of less than 10 ml/min should receive one-half of the dose once a day. Our recommended dosage regimens should produce within the $CL_{CR}$ borderlines of each group average plasma concentrations that are between one and two times that achieved in normal subjects with a t.i.d. dosage regimen.

ACKNOWLEDGMENTS

We acknowledge the expert technical assistance of Guy Fischer and Vreny Trueb.

LITERATURE CITED


