Pharmacokinetics of Intravenous Fusidic Acid in Patients with Cholestasis

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The pharmacokinetics of fusidic acid and 3-ketofusidic acid were investigated in cholestatic and noncholestatic patients after intravenous administration of single and multiple doses of 500 mg of sodium fusidate. The patients, all with low serum albumin levels, were divided into three groups. Group I consisted of six noncholestatic patients; group II consisted of nine mildly cholestatic patients with mild hepatic impairment (conjugated bilirubin, 47 μmol liter−1; alkaline phosphatase, 280 IU liter−1; γ-glutamyltranspeptidase, 190 IU liter−1); group III consisted of six benign intrahepatic cholestatic patients with high isolated conjugated hyperbilirubinemia (98.1 μmol liter−1). Assays were performed by high-pressure liquid chromatography. At steady state, the mean peak concentrations in serum were 63.7, 44.9, and 92.2 μg ml−1 in groups I, II, and III, respectively; over a dosage interval, areas under the concentration-time curve were 411.1, 238.7, and 603.4 μg h ml−1 and the mean body clearances were 0.34, 0.53, and 0.25 ml min kg−1 in groups I, II, and III, respectively. The accumulation ratio of fusidic acid and 3-ketofusidic acid were found in urine. These results substantiate the hypotheses. In group I patients the clearance is higher than that in healthy volunteers because of the increased free, unbound fraction of fusidic acid, a consequence of lower serum albumin concentrations, resulting in increased distribution in tissue and hepatic metabolism. In group III patients, the higher bilirubinemia results in competition with fusidic acid for the limited glucuronidation mechanism, thus compensating for the increased elimination of fusidic acid because of the low serum albumin concentration. These results suggest that fusidic acid can be administered normally even to patients with high bilirubinemia because the postoperative serum albumin concentration is usually low.

Fusidic acid is a steroid-like antibiotic isolated from the fermentation broth of the fungus Fusidium coccineum (8). It is active in vitro against Staphylococcus aureus, Clostridium spp., and corynebacteria (8, 10, 23). Its antibacterial activity is the result of an inhibition of bacterial protein synthesis (1). This drug, which is 95 to 97% bound to plasma albumin (11), is exclusively cleared by hepatic metabolism (9). Fusidic acid is poorly soluble in water (8); therefore, two intravenous formulations have been developed: the diethanolamine salt and the sodium salt. These formulations are more water soluble. Fusidic acid has been shown to be very effective in treating severe staphylococcal infections, including those caused by organisms which are resistant to methicillin (6, 15, 16).

After several days of intravenous treatment with fusidic acid, hyperbilirubinemia and/or elevation of serum alkaline phosphatase activity appears in many cases (6, 12, 15, 16). This side effect occurs particularly if excessive doses are administered and if the drug is infused too rapidly (1). The mechanism of fusidic acid-associated jaundice may be due to intrahepatic cholestasis because of competition with the excretory pathways of hepatic bile acids related to the steroid-like structure of the drug (12, 13). This cholestatic jaundice is reversible either during therapy or shortly after its interruption (12, 16).

Whereas the pharmacokinetics of fusidic acid in healthy volunteers is well documented (22), little is known about the behavior of this drug in infected patients with and without hyperbilirubinemia (18). After major surgery, 16.5% of patients develop mild jaundice and 3.7% develop severe jaundice (5). Two situations are likely to occur in this postoperative period, in which patients are infected as well as jaundiced. The first is intrahepatic cholestasis during infection accompanied by mild clinical signs of hepatic impairment related to fatty liver and preoperative chronic liver disease, in which we note increases in conjugated bilirubin and alkaline hepatic phosphatase and mild signs of hepato-cellular damage (especially increased γ-glutamyltranspeptidase levels, a moderate elevation in aminotransferase levels, and a decrease in the serum albumin concentration) (2, 4, 7); the second is the so-called benign intrahepatic cholestasis, in which spontaneous hemolysis plays a major role and in which the main biological sign is an isolated increase in the amount of conjugated bilirubin (17).

The aim of the present study was to compare the pharmacokinetics of fusidic acid and one of its metabolites, 3-ketofusidic acid, after single and repeated intravenous administration of fusidic acid under a normal dose regimen (500 mg over 2 h every 8 h) in postoperative cholestatic patients and in postoperative noncholestatic patients.

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MATERIALS AND METHODS

Patients. Postoperative patients suffering from pneumonia or septicemia caused by fusidic acid-susceptible staphylococcal strains participated in the study after Ethics Committee approval and the patients' written informed consent were obtained. Seventeen patients were infected with *S. aureus* (13 methicillin-resistant strains and 4 methicillin-susceptible strains), and four patients were infected with methicillin-resistant coagulase-negative staphylococci. A patient was defined as having septicemia when the same strain was isolated in at least two consecutive blood cultures before treatment and the patient's temperature was higher than 38.5°C. A pneumonia was defined by the following: fever, hyperleukocytosis, positive results of clinical examination, purulent tracheal secretion, infiltrate in the X-ray, and positive bacteriological findings obtained by either bronchoalveolar lavage or distal bronchial secretion by fiberoptic bronchoscopy.

The patients, recruited in two Surgical Intensive Care Units at the University Hospital of Strasbourg, were divided into three groups. Group I included nonicteric subjects with bilirubin and serum alkaline phosphatase laboratory values within the normal range; group II included patients with bilirubin, alkaline phosphatase, and γ-nucleotidase activities above the upper limits of normal; and group III included patients with isolated conjugated hyperbilirubinemia.

The following laboratory tests were done pretreatment, on day 3 or 4 after the beginning of treatment, weekly, and posttreatment with fusidic acid to assess the different study groups for purposes of safety assessment and to calculate the simplified acute physiology score prognostic index (14): total bilirubin and conjugated fraction, alkaline phosphatase, γ-nucleotidase, aspartate and alanine aminotransferases, γ-glutamyltranspeptidase, complete blood count with differential leukocyte count, platelet count, glucose, blood urea nitrogen, serum creatinine, arterial blood gas analysis, total protein and serum albumin, blood coagulation profile, and urinalysis. Twenty-one patients entered the study. The demographic, clinical, and biological characteristics of the study population are presented in Table 1. The patients in the three groups were similar with respect to age, weight, and prognostic indices.

Patients with acute liver disease and severe hepatic impairment defined by an increase in the level of aminotransferases of more than twice the upper limit of the normal range were excluded from the study.

To treat severe life-threatening staphylococcal infections and to avoid the emergence of fusidic acid-resistant bacteria, fusidic acid was given in combination (6, 12). To avoid an hepatic reaction, the only concurrent antibiotic chosen was either an aminoglycoside or a glycopeptide (20, 24).

**Study design.** Patients received fusidic acid, 500 mg intravenously over 2 h, every 8 h for at least 4 days. Each vial containing 500 mg of sodium fusidate was dissolved in 10 ml of sterile phosphate-citrate buffer (196 mg of sodium phosphate, 10 mg of citric acid, 5 mg of EDTA), added to 40 ml of saline, and infused via a central venous catheter with an electric pump at uniform speed over a 2-h period. Sodium fusidate was supplied by Laboratoires LEO, Paris, France.

Radial arterial blood samples were collected via a plastic cannula before and at 1.0, 2.0, 2.5, 3.0, 4.0, 6.0, and 8.0 h after the start of infusions 1 and 10. Patients in groups II and III were kept in the study only if their bilirubinemia did not resolve during the 4 days of the study. To ensure that steady-state concentrations in plasma were obtained, the

<table>
<thead>
<tr>
<th>Group and time of analysis</th>
<th>No. of patients (age, Wt. in kg)</th>
<th>Clinical and biological characteristics of the study population*</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Before infusion 1 (6/42)</td>
<td>Age (y) 62.3 ± 18.8, Wt. in kg 63.2 ± 13.5, 10.2 ± 5.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SAPS 5.9, Conjugated bilirubin (μmol liter⁻¹) 4.8 ± 2.6</td>
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<td></td>
<td></td>
<td>Alk. phos. (U/liter⁻¹) 128.2 ± 58.1, AST (U/liter⁻¹) 24.0 ± 14.0</td>
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<tr>
<td></td>
<td></td>
<td>ALT (U/liter⁻¹) 123.4 ± 58.1, Alkaline phosphatase (U/liter⁻¹) 3.3 ± 1.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>γ-GT (U/liter⁻¹) 49.5 ± 2.4, γ-glutamyltranspeptidase (U/liter⁻¹) 5.8 ± 2.7</td>
</tr>
</tbody>
</table>
|                           |                                  | Complete blood cell count, platelet count, glucose, blood urea nitrogen, serum creatinine, arterial blood gas analysis, total protein and serum albumin, blood coagulation profile, and urinalysis. Twenty-one patients entered the study. The demographic, clinical, and biological characteristics of the study population are presented in Table 1. The patients in the three groups were similar with respect to age, weight, and prognostic indices. 

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* Values are mean ± standard deviations. SAPS, simplified acute physiology score; Alk. phos., alkaline phosphatase; γ-GT, γ-glutamyltranspeptidase; ALAT, aspartate aminotransferase; ALT, alanine aminotransferase.

* P < 0.05 versus group I parameter.
FIG. 1. Mean fusidic acid (A, B, and C) and 3-ketofusidic acid (A', B', and C') concentrations in serum versus time in patients in group I (A and A', respectively), group II (B and B', respectively), and group III (C and C', respectively). ●—●, infusion 1; ○—○, infusion 10.

arterial blood samples obtained after infusion 10 were also collected just before and at the end of the 2-h ninth infusion. A urine sample was collected via a bladder catheter just before the 1st and the 10th injections and over the 8-h period from the 1st and the 10th infusions. Serum and urine samples were stored at −70°C until they were analyzed for drug concentrations.

Analytical procedure. The concentrations of both fusidic acid and 3-ketofusidic acid in serum and urine samples and calibration standards were measured as previously described by Sørensen (21) by using a specific reversed-phase high-pressure liquid chromatography (HPLC) assay which was slightly modified.

The diethanolamine fusidate (potency, 98.4%; molecular weight, 621.9), which was used for the preparation of calibration standards of sodium fusidate (molecular weight 538.7), and 3-ketofusidic acid (potency, 99%) were supplied by Laboratoires LEO.
Some 500 µl of serum was deproteinized with an equal volume of acetonitrile, and the solution was mixed for 1 min. After 10 min of centrifugation at 1,000 \times g, 50 µl of clear supernatant was injected into the chromatograph.

Prior to analysis, urine samples were diluted to 1/5 with distilled water and were then injected directly into the chromatograph.

Separations were performed on a high-speed reversed-phase analytical column (75 by 4.6 mm) filled with 3-µm-diameter octadecylsilane-coated silica particles (Beckman). The mobile phase consisted of acetonitrile-acetic acid-water (65:0.3:34.7; vol/vol/vol). The flow rate was set at 1 ml min\(^{-1}\), and the eluent was monitored by measuring the UV absorption at 254 nm. Under these conditions, the retention times of fusidic acid and 3-ketofusidic acid were 3.7 and 3.0 min, respectively. The detection limit of both drugs was 0.2 µg ml\(^{-1}\).

Within- and between-day coefficients of variation at fusidic acid concentrations of 1, 10, and 100 µg ml\(^{-1}\) were 1.1, 3.2, and 0.6% and 6.3, 2.4, and 6.1%, respectively. The method was linear between 0.5 and 100 µg ml\(^{-1}\). The corresponding values for 3-ketofusidic acid at concentrations of 0.5, 1, and 10 µg ml\(^{-1}\) were 5.1, 3.7, and 3.1% and 6.0, 4.5, and 4.0%. The linearity was assessed from 0.5 to 50 µg ml\(^{-1}\).

Pharmacokinetic analysis. During the 1st and 10th doses, the following pharmacokinetic parameters were determined: peak concentration in serum (C\(_{\text{max}}\) and C\(_{\text{10 max}}\)), trough concentration in serum (C\(_{\text{min}}\) and C\(_{\text{10 min}}\)), and area under the serum concentration-time curve over a dosage interval of 0 to 8 h (AUC\(_{0-8}\) and AUC\(_{10-8}\)), as measured by the trapezoidal rule method. The experimental accumulation ratio was estimated as the quotient of AUC\(_{10-8}\)/AUC\(_{0-8}\). For fusidic acid, the body clearance over the 10th dosage interval (0 to 8 h) (CL\(_{10-8}\)) was determined as the quotient of dose/AUC\(_{10-8}\) normalized to body weight.

During the first infusion and at steady state, the trough concentration and the mean concentration in urine, over a dosage interval were determined for fusidic acid and 3-ketofusidic acid. The percentage of renal elimination over a dosage interval was calculated as the quotient of quantitative urine elimination per dose.

Demographic information and biological parameters were described by means, standard deviations, and frequencies. Differences among the three groups were analyzed by analysis of variance. For data showing significance with the analysis of variance, the Fisher test for multiple comparisons was used to assess specific differences. The Mann-Whitney nonparametric test was used when appropriate. Statistical significance was defined to occur at \(P < 0.05\). Linear regression and covariant analyses were performed between clearance and the individual clinical laboratory results for albumin, bilirubin, and alkaline phosphatase concentrations to investigate the relationship between cholestasis and drug disposition.

**RESULTS**

The serum concentration-versus-time curves for fusidic acid and 3-ketofusidic acid obtained after the 1st and the 10th infusions for the three groups of patients are shown in Fig. 1. The corresponding values of C\(_{\text{max}}\) and C\(_{\text{min}}\) are given in Table 2. The differences between the last three trough concentrations in serum (C\(_{10 \text{ min}}\)\(_{C_{\text{max}}}\) and C\(_{10 \text{ min}}\)) or the last two peak concentrations in serum (C\(_{\text{max}}\)\(_{C_{\text{max}}}\) and C\(_{\text{10 max}}\)) in each group were not significant, and steady state seemed to be
TABLE 3. Pharmacokinetic parameters of fusidic acid and 3-ketofusidic acida

<table>
<thead>
<tr>
<th>Group</th>
<th>AUCo.8 (µg · h ml⁻¹)</th>
<th>AUC0-8 (µg · h ml⁻¹)</th>
<th>AUC0-8/AUC0-8</th>
<th>CLIV,0.8 (m³ min⁻¹ kg⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FA</td>
<td>3KFA</td>
<td>FA</td>
<td>3KFA</td>
</tr>
<tr>
<td>I</td>
<td>147.4 ± 17.3</td>
<td>9.1 ± 3.1</td>
<td>411.1b ± 48.6</td>
<td>46.1c ± 20</td>
</tr>
<tr>
<td>II</td>
<td>98 ± 15.5</td>
<td>6.2 ± 4.8</td>
<td>238.7b ± 77.3</td>
<td>23.9e ± 25.2</td>
</tr>
<tr>
<td>III</td>
<td>161.3f ± 41</td>
<td>11.8 ± 5</td>
<td>603.4c± 172.3</td>
<td>61.6g ± 38.4</td>
</tr>
</tbody>
</table>

a Values are means ± standard deviations. FA, fusidic acid; 3KFA, 3-ketofusidic acid; AUC, area under the concentration-time curve; CLIV,0.8, body clearance over the tenth dosage interval.

b P < 0.01 versus group II.

c P < 0.01 versus AUCo.8 in the same group.
d P < 0.05 versus group II.
e P < 0.01 versus group I.

reached by the ninth infusion for both fusidic acid and its metabolite. Comparison of the peak and trough levels of fusidic acid in the three different groups showed a significant decrease in almost all of the values from group I and group III to group II and a significant increase in Cmax and Cmin at steady state from group I to group III.

The AUCo.8 and CLIV,0.8 for fusidic acid and the AUCo.8 for 3-ketofusidic acid are given in Table 3. The difference between the AUC0-8 and AUCIV,0-8 in group II patients was significantly decreased when compared with those in group I and III patients. After repeated administration the experimental accumulation ratio was 2.8 ± 0.2 for fusidic acid and 5.2 ± 1.7 for 3-ketofusidic acid in group I patients, 2.4 ± 0.7 and 5.3 ± 6, respectively, in group II patients, and 4.2 ± 2.2 and 6.3 ± 4.3, respectively, in group III patients (Table 3). In each group, the AUCo.8 values for fusidic acid and 3-ketofusidic acid were significantly increased from interval 1 to interval 10. The body clearance at steady state (CLIV,0.8) was significantly higher in group II patients than in group I and III patients. No correlation could be evidenced between fusidic acid clearance over 8 h and albumin, bilirubin, or alkaline phosphatase concentrations in each group as well as among all the patients considered together. In the same manner, the covariant analysis failed to demonstrate any relationship between clearance and the concentrations of albumin and bilirubin.

Only very small amounts of fusidic acid and 3-ketofusidic acid were found in the urine of patients in the three groups. During the first dosage interval and at steady state, approximately 0.5 mg of fusidic acid could be detected in the urine of the three groups; this corresponded to 0.1% of the infused dose. The metabolite 3-ketofusidic acid could not be detected in the urine of patients in the three groups during the first dosage interval and rose to a maximum of 6% of the corresponding fusidic acid amount excreted in the urine.

DISCUSSION

Despite the usefulness of fusidic acid in the treatment of severe staphylococcal infections, occasional published pharmacokinetic studies have been carried out only in noninfected volunteers (3, 22, 25). Our study provides the first pharmacokinetic data for fusidic acid and 3-ketofusidic acid measured by a specific HPLC method in infected patients with or without intrahepatic cholestasis. All of the previous studies, with the exception of that of Taburet et al. (22), were performed by microbiological assays, which may be inappropriate for an extensively biotransformed drug, the metabolites of which are not well known, particularly concerning the antibacterial activities of the metabolites. Indeed, the major elimination pathway of fusidic acid is hepatic metabolism; this is followed by exclusive biliary elimination of these metabolites. Of the numerous biotransformation products eliminated in bile, the major ones are the glucuron conjugate of fusidic acid, the dicarboxylic metabolite, and a hydroxy derivative of the dicarboxylic metabolite (9). Only very small amounts of fusidic acid and 3-ketofusidic acid are found in bile. Biotransformation occurs only on the free unbound parent molecules, and consequently, any event resulting in an increased free fraction ratio should favor this metabolism.

A common characteristic of our three groups of patients was their low albumin concentrations (Table 1). Because fusidic acid is highly albumin bound (95%), the level of the free fraction may be significantly increased in these patients. This should allow for a larger and faster distribution of the free drug into tissues, together with an increased metabolism, thus leading to a lower concentration and, consequently, to lower AUCs. After the intravenous infusion of the first 500-mg dose of sodium fusidate, previous studies reported mean Cmax of 43.1 µg ml⁻¹ (25), 44 µg ml⁻¹ (3), and 52.4 µg ml⁻¹ (22), which were higher than the peak concentrations in all of our infected patients, regardless of their group. The areas under the serum concentration-time curves were also higher (270 µg · h ml⁻¹ determined by Bergeron et al. [3] and 161 µg · h ml⁻¹ in our study). Of particular interest was the relationship that seemed to exist between the serum albumin concentration and the Cmax of fusidic acid in our three groups of patients. Furthermore, the extrapolation of Cmax to subjects with normal albumin concentrations in serum results in values of the same magnitude as those obtained in healthy volunteers after administration of a single dose (45 to 52 µg ml⁻¹) (3, 22, 25).

At steady state, the CLO,8 in group I and II patients were higher than those in volunteers (0.18 ml min⁻¹ kg⁻¹, as calculated from the data of Taburet et al. [22]), with a lower accumulation ratio (2.8 and 2.4 versus 3.6). This was also certainly due to increased metabolism and a wider distribution resulting from the low albumin concentration. In group II patients, the moderate hyperbilirubinemia had no influence compared with its influence in group I patients. This observation corroborates the fact that fusidic acid does not compete with bilirubin for albumin binding sites (19).

On the contrary, in group III patients, the CLO,8 at steady state was lower than those in group I and II patients, reaching normal values, although albumin concentrations were low. We hypothesize that this is the result of very high bilirubin concentrations through a competition with fusidic acid for participation in the glucuronidation process (12), which is limited. Thus, a lesser amount of fusidic acid can be conjugated, and consequently eliminated in bile, explaining
its accumulation. One must note that the 3-ketofusidic acid/fusidic acid AUC ratio in group III patients (0.10) was similar to those in group I and II patients (0.11 and 0.09, respectively), showing that the chemical biotransformations of the parent drug other than conjugation are not affected even if 3-ketofusidic acid is a minor metabolite. On the contrary, the body clearance (mainly metabolic clearance) is affected by a possible reduced formation of the glucuroconjugate, the major metabolite of fusidic acid.

One must also note that the biotransformation of fusidic acid into 3-ketofusidic acid is not influenced by hyperbilirubinemia.

The results of the present study suggest that, contrary to widely held beliefs (6, 12), fusidic acid can be administered in a normal dosage regimen even to postoperative patients with hyperbilirubinemia in an intensive care unit because their serum albumin concentrations are usually low. This behavior allows maintenance of therapeutic concentrations in these patients, with high concentration/MIC ratios. In addition, the excellent tolerance of the drug used under these conditions allowed its use in all patients (Table 1) throughout the duration of the study.

ACKNOWLEDGMENTS

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REFERENCES