Pharmacokinetics of a Clarithromycin Suspension Administered via Nasogastric Tube to Seriously Ill Patients

Douglas N. Fish and Edward Abraham

Pharmacokinetics of a Clarithromycin Suspension Administered via Nasogastric Tube to Seriously Ill Patients

DOUGLAS N. FISH1* AND EDWARD ABRAHAM2

Department of Pharmacy Practice, School of Pharmacy,1 and Division of Pulmonary Sciences and Critical Care Medicine, School of Medicine,2 University of Colorado Health Sciences Center, Denver, Colorado

Received 10 August 1998/Returned for modification 8 December 1998/Accepted 21 February 1999

The pharmacokinetics of clarithromycin and its 14-(R)-hydroxylated metabolite were studied on two separate occasions after nasogastric administration of 500 mg of a clarithromycin suspension to 16 seriously ill adults in an intensive care unit. The clarithromycin suspension appeared to be adequately absorbed, and the pharmacokinetics of neither clarithromycin nor 14-(R)-hydroxylclarithromycin differed significantly between the two dosing periods. No substantial differences in pharmacokinetics were observed compared to previously published studies of other adult populations. Minimal intrapatient variability of pharmacokinetic parameters was observed in these seriously ill patients.

Clarithromycin is a semisynthetic macrolide antimicrobial which has activity against a wide range of pathogens, including methicillin-susceptible Staphylococcus aureus, Streptococcus pneumoniae and other streptococci, Haemophilus influenzae, Chlamydia pneumoniae, Mycoplasma pneumoniae, and Legionella spp. (7, 11–13, 21). Clarithromycin’s principal metabolite, 14-(R)-hydroxylclarithromycin (14-OH-clarithromycin), also possesses antibacterial activity and has been reported to be more active than the parent drug against many strains of H. influenzae (14, 16). Clarithromycin has been shown to be effective in the treatment of a variety of community-acquired infections, including upper and lower respiratory tract and skin and skin structure infections (15, 19).

Although clarithromycin is potentially useful in the treatment of many community-acquired infections, the use of this agent in seriously ill patients has been limited in part by the lack of a parenteral formulation of the drug. However, clarithromycin may perhaps have a potential role as one component of intravenous-to-oral conversion (switch therapy) programs. These programs have been demonstrated to be clinically effective and are gaining widespread acceptance as a means of facilitating early discharge of patients from the hospital and reducing overall costs of antimicrobial therapy (1, 9, 17, 18, 20, 23). Clarithromycin may potentially be included in intravenous-to-oral conversion regimens, and a clarithromycin suspension may also have a potential role in the early transition to oral medications in patients unable to receive solid oral dosage forms. However, clarithromycin has never been studied in seriously ill patients in this regard and it is unknown whether the absorption of clarithromycin is adequate in such patients. The objective of the present study was to examine the absorption and pharmacokinetics of a clarithromycin suspension administered via nasogastric tube to seriously ill patients in an intensive care unit (ICU).

(This work was presented, in part, as abstract A79 at the 36th Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans, La., in September 1996 [10].)

This was an open-label study of clarithromycin (Abbott Laboratories, Abbott Park, Ill.) and its principal metabolite, 14-OH-clarithromycin. Adult patients between the ages of 18 and 70 who were hospital inpatients in an ICU and had a nasogastric tube in place were considered eligible for enrollment in this study. Exclusion criteria included pregnancy or child-bearing potential if female, history of hypersensitivity to any macrolide antibiotic, evidence of significant gastrointestinal dysfunction (e.g., absent bowel sounds, ileus, high gastric fluid residuals, etc.), evidence of severe renal impairment (creatinine clearance of <30 ml/min calculated by the method of Cockcroft and Gault [6]), evidence of significant hepatic dysfunction, and concomitant treatment with any drug which might interact with clarithromycin (e.g., theophylline, warfarin, carbamazepine, or digoxin). The study was approved by the Institutional Review Board of the hospital where the study was performed, and written informed consent was obtained from each patient or a legally designated representative prior to study entry. All nasogastric tubes were placed as part of the necessary medical care of the patients and were not placed solely for the purpose of participation in this study.

Patients enrolled in the study received 500-mg doses of a clarithromycin suspension via nasogastric tube on each of two occasions. Two separate study periods were utilized in order to assess intrapatient variation in clarithromycin absorption and plasma pharmacokinetics. Study days were separated by a washout period of at least 72 h. A complete medical history was obtained for each enrolled patient, and a complete physical examination and a laboratory review of serum chemistry and hematologic findings were performed and reviewed prior to administration of the study medication. Clarithromycin was administered as a single dose on the morning of each day on which blood samples were obtained. Clarithromycin was prepared as a suspension at a concentration of 250 mg/5 ml and was instilled into the nasogastric tube by using an oral syringe. Patients receiving nasogastric nutritional supplements, sucralate, or antacids had these agents withheld for at least 4 h prior to administration of each clarithromycin dose due to the uncertain potential for interference with clarithromycin absorption. Nasogastric tubes were flushed with 30 ml of water following clarithromycin administration in order to ensure complete delivery of the full dose of medication, and the tubes were subsequently clamped for 2 h following administration of the drug. Concurrent medications (i.e., sucralfate, antacids, and nutritional supplements) were also withheld during this period.
2-h postdose period. Samples of blood (7 ml) were obtained from each patient at time zero (prior to dosing) and again at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, and 24 h following administration of the clarithromycin dose on each study day.

Blood samples were collected into heparinized tubes and promptly centrifuged. Plasma was then transferred to labeled polyethylene vials and frozen at −70°C until assayed. Parent drug and metabolite concentrations in plasma were determined by high-performance liquid chromatography with electrochemical detection using an adaptation of a previously published procedure (3). Standard-curve concentration ranges were 0.04 to 6.0 μg/ml for both clarithromycin and 14-OH-clarithromycin. Samples with concentrations greater than the upper limit of the standard curve were reanalyzed at a reduced volume. Coefficients of determination ($r^2$) for the curves of both clarithromycin and 14-OH-clarithromycin were in the range of 0.997 to 0.999 for the entire study. The lower limits of detection were 0.04 μg/ml for both compounds. For this study, the inter- and intraday coefficients of variation over the standard-curve concentration ranges were ≤3.8 and ≤2.9% for clarithromycin and ≤4.6 and ≤4.2% for 14-OH-clarithromycin, respectively.

Plasma concentration-time data for clarithromycin and 14-OH-clarithromycin were analyzed by standard noncompartmental methods. Peak drug concentrations in plasma ($C_{max}$) and the times at which these concentrations were achieved ($T_{max}$) were estimated by visual inspection of the plasma concentration-versus-time data. Elimination was assumed to be first order. The apparent terminal elimination rate constant ($k_{el}$) was determined by least-squares regression analysis of the terminal portion of the natural log concentration-time curve. Elimination half-life in plasma ($t_{1/2}$) was calculated as 0.693/$k_{el}$. The area under the plasma concentration-time curve from time zero to infinity ([AUC }_{0–\infty}) was calculated as [AUC }_{0–last} + ($C_{last}$/ $k_{el}$), where [AUC }_{0–last} is the AUC from time zero to the last measured drug concentration in plasma (calculated by the linear trapezoidal summation method) and $C_{last}$ is the last measured drug concentration in plasma. Apparent total systemic clearance (CL/F) was calculated as dose/[AUC }_{0–\infty}, and the apparent volume of distribution ($V_{area}$) was calculated as dose/($k_{el}$ × [AUC }_{0–\infty}). We were not able to calculate the CL/F and $V_{area}$ of 14-OH-clarithromycin due to lack of definitive information regarding the extent of clarithromycin biotransformation and because the equivalent “dose” of this metabolite was unknown.

Differences in clarithromycin and 14-OH-clarithromycin concentrations in plasma and calculated pharmacokinetic parameters between the two study periods were assessed for statistical significance by the two-tailed Wilcoxon signed-rank test for paired nonparametric data (SPSS 8.0 for Windows; SPSS, Inc., Chicago, Ill.). A $P$ value of ≤0.05 was considered significant.

Eighteen hospitalized patients admitted to the medical ICU were enrolled in this study. Sixteen patients (seven males and nine females) completed both study periods and are included in this report. The two patients who failed to complete the study had nasogastric tubes removed and were transferred out of the medical ICU prior to completing the second dosing period.

![FIG. 1. Mean plasma clarithromycin concentration-time profiles following the administration of single 500-mg oral doses of a clarithromycin suspension via nasogastric tube to seriously ill patients on study days 1 and 4. Error bars represent SDs.](http://aac.asm.org/1278)
The mean (± standard deviation [SD]) age, weight, and creatinine clearance of these patients were 50.1 ± 11.4 (range, 31 to 67) years, 73.3 ± 10.5 (range, 48.9 to 88.4) kg, and 86 ± 18 (range, 42 to 121) ml/min, respectively. Hepatic function tests and gastrointestinal function were assessed to be within normal limits in all patients. Reasons for ICU admission were pneumonia (10 patients), exacerbation of chronic bronchitis (2 patients), urosepsis (1 patient), lung abscess (1 patient), meningioma (1 patient), and disseminated aspergillosis (1 patient). The mean ± SD APACHE II score for enrolled patients was 19 ± 4 (range, 11 to 24). The study drug was well tolerated by all of the patients, and no adverse effects were reported or detected.

The mean plasma concentration-time curves for the two study periods are illustrated in Fig. 1 (clarithromycin) and 2 (14-OH-clarithromycin). Single-dose concentrations of clarithromycin and 14-OH-clarithromycin obtained by high-performance liquid chromatography for both study periods are shown in Table 1. The clarithromycin suspension appeared to be adequately absorbed following nasogastric administration, with a clarithromycin T\text{max} of 3.5 ± 0.8 h on the first study day. The mean C\text{max} of clarithromycin and 14-OH-clarithromycin on the first study day were 2.1 ± 0.9 (range, 1.8 to 4.4) µg/ml and 0.9 ± 0.3 (range, 0.4 to 1.4) µg/ml, respectively. The second study period was begun 72 h following the initial dosing period for all patients except two; the second study period occurred after 96 h for these patients. There were no statistically significant differences between the concentrations of either clarithromycin or 14-OH-clarithromycin in plasma between the two study periods (Table 1). There were also no statistically significant differences in T\text{max}, AUC\text{0–}\infty, CL/F, V\text{area}, or t\text{1/2} between the two study periods, indicating minimal intrapatient variability in the disposition of these two compounds within the patients studied. Post-hoc analysis showed that the abilities of this study to detect a statistically significant difference (P < 0.05) in C\text{max} or AUC\text{0–}\infty between the two study periods were 0.88 and 0.82, respectively.

Although the mean T\text{max} was slightly delayed and the mean C\text{max} was somewhat decreased in the present study, the clarithromycin and 14-OH-clarithromycin C\text{max} of 2.1 and 0.9 µg/ml, respectively, were comparable to those previously reported for studies of clarithromycin pharmacokinetics in adult volunteers or less severely ill adults (4, 5, 8, 22). Other pharmacokinetic parameters were also similar to those previously reported. These data indicate that the absorption of a clarithromycin suspension is adequate after administration via nasogastric tube and that there was good intrapatient consistency in the absorption and disposition of clarithromycin in this seriously ill ICU population.

It should be noted that the subjects in this study were relatively stable, with no significant organ (i.e., renal, hepatic, or gastrointestinal) dysfunction. These subjects are therefore not necessarily representative of many severely ill ICU patients, in whom dysfunction of these organs is quite common. Gastrointestinal dysfunction resulting from underlying disease states, surgery, drugs, or other causes would be anticipated to predi-
pose to difficulties in the absorption of oral medications such as clarithromycin (2). In addition, significant renal and/or hepatic dysfunction would also be expected to lead to alterations in the pharmacokinetics of certain drugs. However, patients suitable for inclusion in intravenous-to-oral switch programs are generally relatively stable and not dissimilar to the patients enrolled in this study (1, 9, 17, 18, 20).

This study provides the basis for consideration of the use of a clarithromycin suspension as part of intravenous-to-oral switch regimens for the management of infectious diseases caused by susceptible pathogens in appropriately selected ICU patients. Additional studies are required to demonstrate the actual clinical efficacy of a clarithromycin suspension in this setting. However, based on these pharmacokinetic data, a clarithromycin suspension may provide a possible cost-saving option for selected patients in whom switch therapy including a macrolide is desirable but who are not yet able to switch from an intravenous to a solid oral dosage form.

This work was supported by a grant from Abbott Laboratories.

REFERENCES


TABLE 1. Pharmacokinetic parameters of clarithromycin and 14-OH-clarithromycin in 16 patients in an ICUa

<table>
<thead>
<tr>
<th>Drug and time</th>
<th>Cmax (µg/ml)</th>
<th>Tmax (h)</th>
<th>Cmax (µg/ml)b</th>
<th>AUC0–∞ (µg · h/ml)</th>
<th>t1/2 (h)</th>
<th>CL/F (ml/min)</th>
<th>Varea (liters)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarithromycin Day 1</td>
<td>2.1 (0.9)</td>
<td>3.5 (0.8)</td>
<td>0.1 (0.1)</td>
<td>17.6 (2.8)</td>
<td>4.3 (0.5)</td>
<td>473.0 (75.2)</td>
<td>176.3 (28.0)</td>
</tr>
<tr>
<td>Day 4</td>
<td>2.3 (0.6)</td>
<td>3.3 (0.6)</td>
<td>0.1 (0.1)</td>
<td>18.2 (2.6)</td>
<td>4.4 (0.6)</td>
<td>457.6 (65.4)</td>
<td>174.4 (24.9)</td>
</tr>
<tr>
<td>P value</td>
<td>0.58</td>
<td>0.43</td>
<td>0.62</td>
<td>0.53</td>
<td>0.61</td>
<td>0.54</td>
<td>0.84</td>
</tr>
<tr>
<td>14-OH-clarithromycin Day 1</td>
<td>0.9 (0.3)</td>
<td>4.4 (0.5)</td>
<td>0.2 (0.1)</td>
<td>10.6 (1.5)</td>
<td>7.9 (1.7)</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Day 4</td>
<td>1.0 (0.4)</td>
<td>4.3 (0.8)</td>
<td>0.2 (0.1)</td>
<td>11.4 (1.8)</td>
<td>8.1 (0.7)</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>P value</td>
<td>0.65</td>
<td>0.68</td>
<td>0.22</td>
<td>0.18</td>
<td>0.67</td>
<td>0.18</td>
<td>0.39</td>
</tr>
</tbody>
</table>

a A clarithromycin suspension was administered as single 500-mg doses via nasogastric tube to seriously ill patients on study days 1 and 4. The data are means, and SDs are in parentheses.

b Cmax, concentration in plasma at 24 h after dosing.

c Not able to be calculated.