A common rationale for the administration of antibiotics via the IV route, rather than the oral route, is the concern that there may be a diminished ability to absorb medications when the patient is acutely ill.1 Usually, patients admitted to the hospital for the treatment of community-acquired pneumonia (CAP) are initially treated with IV antibiotics and, once the acute stage of their illness has passed, are then converted to oral antibiotic therapy.2 While undoubtedly ensuring delivery, the use of IV antibiotics is potentially associated with decreased patient mobility, increased patient discomfort, increased length of stay, increased treatment costs, and an increased risk of catheter-associated infections.2,3

Clarithromycin is a broad-spectrum, oral, macroclide antibiotic that has in vivo antibacterial activity against many of the pathogens associated with CAP.4–6 According to published guidelines, macrolides are among the drugs used for first-line therapy for many patients with CAP.5,6 In small, randomized clinical trials, the combination of oral clarithromycin and IV cefuroxime has compared favorably to the combination of IV erythromycin and IV cefuroxime.7,8 The oral clarithromycin combination of-

**Study objective:** To compare the extent of oral clarithromycin absorption in patients during an illness and in health.

**Design:** Sequential two-phase prospective study including an acutely ill pneumonia phase (PP) and a subsequent convalescent phase (CP).

**Study population:** Patients ≥18 years old with radiographically confirmed community-acquired pneumonia (CAP) who were admitted to the hospital.

**Methods:** During both study phases, patients received one single 500-mg dose of oral clarithromycin. Serial blood samples were drawn over a 24-h period in order to characterize the plasma concentration-time curves. Area under the curve from zero to 24 h (AUC0–24), maximum plasma concentration (Cmax), and time to maximum concentration (Tmax) were determined for both clarithromycin and its metabolite, 14-hydroxyclarithromycin, and compared between the two phases.

**Results:** Twelve patients completed both phases of the study. For clarithromycin, there was a significant increase in AUC0–24 (47.37 ± 8.51 μg·h/mL vs 36.22 ± 6.09 μg·h/mL) in favor of the PP. There were no significant differences detected with respect to Cmax (4.32 ± 0.63 μg/mL vs 3.57 ± 0.46 μg/mL), or Tmax (3.50 ± 0.50 h vs 2.83 ± 0.59 h) between PP and CP. For 14-hydroxyclarithromycin, the AUC0–24 and Cmax were significantly higher (5.84 ± 1.08 μg·h/mL vs 8.84 ± 1.92 μg·h/mL; 0.42 ± 0.08 μg/mL vs 0.76 ± 0.23 μg/mL) in the CP as compared to the PP. Tmax remained unchanged.

**Conclusion:** The extent of absorption of oral clarithromycin was not diminished during an acute illness with CAP. (CHEST 2000; 117:1090–1093)

**Key words:** acute illness; clarithromycin; community-acquired pneumonia; pharmacokinetics

**Abbreviations:** AUC = area under the curve; AUC0–24 = area under the plasma concentration vs time curve from zero to 24 h; CAP = community-acquired pneumonia; Cmax = maximum plasma concentration; CP = convalescent phase; PP = pneumonia phase; Tmax = time to maximum concentration

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ferred some advantages with respect to clinical cure, microbiologic cure, and cost of treatment.

The objectives of this study were to determine the impact of acute illness with CAP on the extent of oral absorption of clarithromycin, and to compare it to the extent of oral absorption in health.

**MATERIAL AND METHODS**

This was a two-phase prospective study, whereby hospitalized patients participated in an acute illness phase termed the pneumonia phase (PP), and a convalescent phase (CP). The PP of this study included patients ≥ 18 years old who were enrolled within 36 h of admission to hospital, and had a diagnosis of pneumonia based on clinical and radiographic findings. Patients were excluded from the study if they were unable to sign informed consent; had a documented GI malabsorption syndrome; were pregnant or lactating; had excessive nausea or vomiting; had a known allergy to clarithromycin or other macrolide antibiotics; had known hepatic or end-stage renal disease; or had completed a course of a macrolide antibiotic within 2 weeks prior to admission. Patients were then asked to return for the second phase of the study (CP), a minimum of 2 weeks after hospital discharge for their pneumonia. Using a standard drug interaction text, all medications at enrollment were assessed for the potential to interact with clarithromycin. Medications that could potentially impede the absorption, or affect the plasma concentration of a single oral dose of clarithromycin were held for the study period. If it was not feasible to hold these medications, patients were excluded from the study.

On enrollment to the PP, patients were evaluated for their severity of illness, using a previously published prediction rule to identify risk of mortality of patients with CAP. After obtaining informed consent, patients received one single oral dose of clarithromycin, 500 mg, in addition to antibiotic therapy for CAP, prescribed at the discretion of the attending physician. Antibiotic therapy for CAP did not include a macrolide antibiotic, and generally consisted of IV cefuroxime, 750 mg q8h. Patients had no oral intake for approximately 6 h before and 4 h after the dose. Blood samples were obtained in heparinized tubes either by direct venipuncture, or via a catheter inserted into the antecubital vein, immediately prior to the dose, and 1, 2, 3, 4, 8, 12, 16, and 24 h after administration of the dose. Plasma was separated, and stored at −20°C until assayed for concentrations of clarithromycin and its metabolite, 14-hydroxyclarithromycin. When the patients returned for the CP of the study, a second single oral dose of clarithromycin, 500 mg, was administered, and serial blood samples were obtained at the same time points as previously stated. As with the PP, patients had not received clarithromycin within 2 weeks prior to the CP.

Plasma samples were assayed using a high-performance liquid chromatographic technique described elsewhere. The lower limit of detection of this assay is 0.03 µg/mL, using 0.5 mL of plasma. The calibration curves for the determination of clarithromycin and its metabolite were found to be linear in the range of 31.25 to 6,000 ng/mL and 7.8 to 1,000 ng/mL, respectively, with consistent slopes and correlation coefficients \( r^2 \geq 0.9927 \) throughout the validation runs. Inter-day assay variability was ≤ 6.4%, and intra-day assay variability was ≤ 7.2% for all standards evaluated. The mean accuracy was 102%. The mean recovery was found to be 97% for clarithromycin and 92% for 14-hydroxyclarithromycin.

The study protocol was approved by the University of Western Ontario Review Board for Health Sciences Research Involving Human Subjects, London, Ontario, Canada. Written informed consent was obtained from all patients prior to enrollment.

<table>
<thead>
<tr>
<th>Group</th>
<th>AUC(_{0–24}), µg/h/mL</th>
<th>Cmax, µg/mL</th>
<th>Tmax, h</th>
</tr>
</thead>
<tbody>
<tr>
<td>PP</td>
<td>47.37 ± 8.51</td>
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<td>3.50 ± 0.50</td>
</tr>
<tr>
<td>CP</td>
<td>36.22 ± 6.09</td>
<td>3.57 ± 0.46</td>
<td>2.83 ± 0.59</td>
</tr>
<tr>
<td>p value</td>
<td>0.075</td>
<td>0.231</td>
<td>0.369</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SEM unless otherwise indicated.

**RESULTS**

Eight male and four female patients (mean age, 77 ± 2 years) participated in both phases of the study, and were included in the analysis. The mean weight of the subjects was 64 ± 5 kg, and the mean creatinine clearance was 49 ± 6 mL/min. As previously mentioned, all patients included in the study were evaluated on admission for severity of illness using a prediction rule for identifying risk of patients with CAP. The 12 patients enrolled in the present study had a mean ± SEM severity of illness score of 101.5 ± 6.9, suggesting that they were at high risk for mortality, and therefore acutely ill. The mean values of clarithromycin and its metabolite for AUC\(_{0–24}\), Cmax, and Tmax of both the PP and CP are reported in Tables 1, 2. With respect to clarithromycin, the AUC\(_{0–24}\) was greater in the PP than in

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**Data Analysis**

The goal of the study was to show that the area under the plasma concentration vs time curve from zero to 24 h (AUC\(_{0–24}\)) was not statistically different between the CP and PP. Assuming an alpha error of 0.05 at 80% power, eight patients were required per arm to achieve statistical significance. A difference of < 30% in plasma concentration of clarithromycin (or metabolite) was believed to be acceptable, as this generally yields plasma concentrations above the minimum-inhibitory concentration 90% (MIC\(_{90}\)) for the majority of pathogens typically causing CAP.

Plasma concentration-time curves were plotted to assist in determining AUC\(_{0–24}\) which was calculated using the linear trapezoidal rule. Individual maximum plasma concentration (Cmax) and time to maximum concentration (Tmax) values were determined by visual inspection of the plasma concentration data. The primary endpoint of AUC\(_{0–24}\) (in micrograms per hour per milliliter) and the secondary endpoints of Cmax (in micrograms per milliliter) and Tmax (in hours) were compared between the PP and CP by using a computer statistics program. Normality of the data distribution was assessed using a Kolmogorov-Smirnov test. For data that passed the normality test, comparison between the two groups was done using two, one-tailed t tests. By setting the significance level at 10% for the two-tailed paired t test, the probability of accepting the null hypothesis of no difference is reduced, and therefore provides a more stringent means of providing evidence that the two groups are in fact similar. This would be analogous to using two, one-tailed t tests at the 5% level. Data that failed the normality test were compared using the Wilcoxon signed rank test. As the two-tailed significance level was set at 10% for this comparison, a value of p < 0.05 was considered to be significant. Results are reported as mean ± SEM.
There were no differences detected between the two phases for Cmax and Tmax. With respect to the metabolite 14-hydroxyclarithromycin, a significant difference in AUC0–24 and Cmax was detected between the two groups in favor of the CP. There was, however, no difference detected between the two phases for Tmax.

Figures 1, 2 depict the mean ± SEM plasma concentration of clarithromycin and its metabolite at each sampling time vs time for both the PP and CP.

**DISCUSSION**

This study demonstrates that the extent of clarithromycin absorption is altered in patients who are acutely ill with CAP when compared to the same patients following their convalescence. The presence of active CAP appears to significantly increase the AUC0–24 of clarithromycin, when a single oral dose of clarithromycin is administered. However, active CAP appears to decrease the AUC0–24 and Cmax of the metabolite, 14-hydroxyclarithromycin.

The results of this trial are supported by two other studies examining the impact of acute illness on the pharmacokinetic parameters of oral antibiotics. Dean et al. assessed the absorption of a single 500-mg dose of cephalexin in patients who were acutely ill, and compared this to the absorption of patients who were hospitalized but not acutely ill. Results showed no significant differences between the two groups of patients in Cmax or Tmax of cephalexin. There was a slightly delayed urinary excretion time and an increased half-life in the acutely ill group; however, this difference did not reach statistical significance.

Guay et al. determined the pharmacokinetic parameters after multiple doses of ciprofloxacin in elderly patients during an acute illness. Thirteen patients were evaluated for area under the curve (AUC), peak serum concentration, clearance, terminal half-life, and volume of distribution at the beginning of their illness, and again during their convalescence. There were no significant differences detected in any of these parameters between the two phases. There was, however, a trend toward an increased peak serum concentration in the convalescent phase, and a trend toward an increased AUC in the acutely ill phase. In our study, there was an increased AUC0–24 in the acutely ill phase, which is similar to what Guay et al. observed.

Unlike the previously mentioned studies, a significant difference was, in fact, detected between the two groups with respect to AUC. This, along with a lower AUC0–24 of the major metabolite in the PP compared to the CP may indicate that clearance of the parent compound may be altered or delayed in the acute phase of an illness such as pneumonia. There was a trend to this seen in the earlier described study by Dean et al., which is similar to our observations. Changes in renal clearance are less likely to be involved given the small proportion of

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**Table 2—Pharmacokinetic Parameters of 14-OH Clarithromycin for Patients During PP and CP**

<table>
<thead>
<tr>
<th>Group</th>
<th>AUC0–24, µg/h/mL</th>
<th>Cmax, µg/mL</th>
<th>Tmax, h</th>
</tr>
</thead>
<tbody>
<tr>
<td>PP</td>
<td>5.84 ± 1.08</td>
<td>0.42 ± 0.08</td>
<td>4.83 ± 1.29</td>
</tr>
<tr>
<td>CP</td>
<td>8.54 ± 1.92</td>
<td>0.76 ± 0.23</td>
<td>3.08 ± 0.51</td>
</tr>
<tr>
<td>p value</td>
<td>0.033</td>
<td>0.027†</td>
<td>0.322†</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SEM unless otherwise indicated.
†Data which was compared by nonparametric statistical test (Wilcoxon signed rank).
clarithromycin that is cleared renally (approximately 30%). Davey reported that there is a progressive increase in serum concentrations of clarithromycin and 14-hydroxylactithromycin with renal impairment (defined as a glomerular filtration rate < 30 mL/min). Of our patients who had documented renal disease, changes in renal clearance accounting for the changes in AUC0–24 are most unlikely.

Clarithromycin undergoes extensive first-pass hepatic metabolism, and as there may be altered or slowed blood flow in an acute illness, it may be accompanied by a decrease in first-pass metabolism of the parent compound, and a decreased generation of the metabolite. The result, a decrease in the metabolism of clarithromycin, would be both an increase in serum level of the parent compound and a decrease in the serum level of the metabolite. The implications of a decrease in the generation of the active metabolite are unknown. However, if it were simply a delay, an equivalent AUC would be achieved after repeated dosing.

With respect to this study, an important point to consider is the effect of concomitant medications on the pharmacokinetics of clarithromycin. As mentioned, medications that were known to affect gut motility, or have an effect on the pharmacokinetics of clarithromycin, were held during the dosing period. In the convalescent phase, one patient insisted on smoking cigarettes, of which the effect on clarithromycin is not known.

In this study, there was significant interindividual variability in the results. Reasons for this can include a small sample size, but more importantly a large variability in the concomitant disease states found in the subjects. As it was difficult to enroll subjects when their only reason for admission was CAP, there tended to be a variety of other factors that could not be controlled for in this particular study. Further studies may be needed to evaluate the impact of concomitant illness on the pharmacokinetic parameters of clarithromycin in CAP.

Current guidelines suggest the use of IV antibiotics for a variable length of time, and the use of a second- or third-generation cephalosporin in combination with a macrolide antibiotic. This study suggests that the bioavailability of oral clarithromycin for patients admitted to hospital for the treatment of CAP is adequate.

**Conclusion**

The oral absorption of clarithromycin is not impaired in patients who are acutely ill with CAP.

**References**