Clarithromycin was developed to provide prescribers with a macrolide that is better tolerated and that has a broader spectrum of activity and a more favorable pharmacokinetic profile than were available with erythromycin. The use of clarithromycin has been shown to result in fewer gastrointestinal side effects and to have increased and predictable absorption compared to those from the use of erythromycin (16). It has also been demonstrated to have a broader spectrum of activity. Through the metabolism of clarithromycin by CYP3A4, approximately 25% of the systemically bioavailable drug is converted to an active metabolite, 14-OH-clarithromycin (14OHC) (3). Despite the minor inherent activity of clarithromycin against Haemophilus influenzae, 14OHC has been demonstrated to have significant antibacterial activity against this key community-acquired gram-negative pathogen. However, like any drug that is dependent on the production and the activity of a metabolite, clarithromycin’s activity against H. influenzae is variable (20 to 100%) (1, 4, 6, 12–14, 17).

In terms of safety, the one aspect that has not been improved is the preponderance of drug interactions. Clarithromycin is an inhibitor of CYP1A2 and CYP3A4, which has resulted in significant interactions with several drugs such as terfenadine, carbamazepine, theophylline, and zidovudine, to name a few (2). As much as clarithromycin interacts with these metabolic pathways, it is just as susceptible to metabolic inhibition and induction. This has been demonstrated with such drugs as rifabutin and rifonavir (2). Due to its current use with several acid-secreting antagonists both in patients being treated for respiratory tract infections and in patients with Helicobacter pylori infections, it has been necessary to ensure a lack of interaction between these agents.

To date, neither omeprazole nor ranitidine has been shown to negatively interact with clarithromycin (2, 11). A study with cimetidine has yet to be reported. The present study was conducted due to the high-volume use of prescription and nonprescription cimetidine and clarithromycin and the potential for their concurrent use. The hypothesis on entering the study was that due to the broad and nonspecific inhibitory effects of cimetidine on the cytochrome P-450 metabolic system, there would be a significant decrease in the production of 14OHC.

MATERIALS AND METHODS

The protocol used for the present study was approved by the Institutional Review Board of Bassett Healthcare. Twelve subjects were enrolled. All subjects provided written informed consent. All subjects were healthy as determined by medical history, physical examination, and laboratory screening (a complete blood count, serum chemistries, urinalysis, and serum pregnancy tests for women of childbearing potential). Subjects had to be at least 19 years of age and free of exposure to any drug except acetaminophen for at least 10 days prior to the study period. Exclusion criteria included a sensitivity to macrolides or H₂-antagonists or serious allergic reaction to any other medication; a history of blood dyscrasia; a recent history of drug or alcohol abuse; use of astemizole 30 days prior to the study; use of terfenadine, loratadine, or cisapride 14 days prior to the study; and use of nicotine delivery systems in the past 12 months. All screening blood work was repeated after the last phase of the study to document any adverse effects according to laboratory test results.

This was an open-label, randomized, crossover study. By a random-number table (10), subjects were assigned to the following treatment regimens in random order: (i) a single 500-mg dose of clarithromycin (Biaxin; lot no. 14-905-1A; 21; expiration date, 1 April 1998; Abbott Laboratories) with 240 ml of water and (ii) three doses of 800 mg of cimetidine (Tagamet; lot no. 8046T27 and 8085T27; expiration dates, 30 June 1998 and 31 December 1997, respectively; SmithKline Beecham) 12 h with a single 500-mg dose of clarithromycin administered with 240 ml of water at 0.5 h (approximate time to maximum serum cimetidine concentrations) after administration of the last cimetidine dose. Subjects fasted for at least 8 h prior to the administration of each clarithromycin dose and for the subsequent 4 h after its administration. No alcohol or caffeine was allowed during the study. Subjects were instructed to avoid citrus beverages, citrus fruits, cruciferous vegetables, charbroiled meats, and fatty foods during the study period. Dosing phases were separated by a 7-day washout period.

Blood was sampled prior to clarithromycin dosing and at 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 8, 12, 24, 48, and 72 h after its administration. After centrifugation, serum was harvested and stored at −80°C until assay. The concentrations of clarithromycin and 14OHC in serum were assayed by a validated high-pressure liquid chromatography (HPLC) assay. The HPLC assay was performed with a Waters model 510 pump and a model 680 gradient-controlled and solvent selector valve; a Spectra Physics model 8875 fixed-volume autosampler, an ESA Couloumec II electrochemical detector, a Macintosh 7100 computer, and the Ranin Dymaxx HPLC data management system. The standard curves for the concentrations of clarithromycin and 14OHC in serum ranged from 0.20 to 10.00 and 0.18 to 4.42 mg/liter, respectively. The fits of the standard curves were achieved by using a weighting scheme of \( y^2 \). The coefficients of determination \( (R^2) \) for the standard curves all exceeded 0.998. The recovery of clarithromycin from serum was 101.1% (range, 98.3 to 103.3%). Testing for clarithromycin within sample precision produced a coefficient of variation of 1.9%. Testing for 14-OH-clarithromycin produced a coefficient of variation of 3.7% (low, 0.9%; at 5.0 mg/liter; high, 7.5% at 0.5 mg/liter). Similar parameters were determined for 14OHC.

Serum clarithromycin and 14OHC concentration data were analyzed via noncompartmental analysis with TOPFIT, version 2.0 (19), and a weighting scheme of \( y^2 \). Parameters obtained from the analysis included peak concentration \((C_{max})\), time to \( C_{max} \) (\( T_{max} \)), area under the serum concentration–time curve from zero time to infinity \((AUC_{0–\infty})\), half-life \((t_{1/2})\), apparent total oral clearance \((CL/F)\) [with \( F \) denoting bioavailability], and elimination rate constant \((k_e)\). A power calculation with an \( \alpha \) level of 0.05, a \( \beta \) level of 0.10, and an estimated clinically significant 25% change in the test group found that a sample size of 12
respectively); this resulted in significant increases in their
estimated creatinine clearance, 85.9 ml/min/1.73 m$^2$
(75% [9]) completed both arms of the study. The adverse effects experienced by the subjects were comparable to those experienced in previous studies with clarithromycin, with mild gastrointestinal upset (25%) and taste perversion (33%) being the most common (7, 8).

Compared to the control arm, steady-state oral cimetidine prolonged the absorption of clarithromycin. This was evidenced by a 46% decrease in the $C_{\text{max}}$ of clarithromycin (2.42 versus 1.30 mg/liter; $P < 0.001$) and a 43% decrease in that of 14OHC (1.16 versus 0.68 mg/liter; $P < 0.001$) (Fig. 1 and 2). The interaction also demonstrated a 68% increase in the $T_{\text{max}}$ of 14OHC (1.39 versus 2.34 h; $P = 0.04$). $k_{\text{es}}$s were also decreased for both compounds (36% [$P = 0.002$] and 35% [$P = 0.005$], respectively); this resulted in significant increases in their $t_{1/2}$s (75% [$P = 0.006$] and 82% [$P = 0.009$], respectively). Despite these changes, there was no significant difference in CL/F or AUC$_{\text{0-}\infty}$ between the control and cimetidine study arms for both clarithromycin and 14OHC (Table 1).

**DISCUSSION**

This study initially set out to identify whether there was a hepatic CYP3A4 interaction between cimetidine, dosed to steady state, and clarithromycin-14OHC. The results of the study indicated that although there was no metabolic drug-drug interaction between the two compounds, as evidenced by unchanged CL/F and AUCs for both clarithromycin and 14OHC, a different sort of interaction was evident. The results of the study indicate that cimetidine may prolong the absorption of clarithromycin and thereby delay the production of 14OHC (increased $T_{\text{max}}$ of 14OHC by 68%). This prolongation of the absorption of clarithromycin resulted in significant decreases in the peak concentrations of both the parent and active metabolite compounds in serum.

The mechanism for this unexpected interaction is unknown. Previous studies have shown that clarithromycin's absorption is unaffected by the changes in gastric pH induced by omeprazole and ranitidine (2, 11). It is therefore unlikely that the results seen in this study are secondary to the pH changes induced by the high dose of steady-state cimetidine. Rather, it may be hypothesized that there is either competition between the two compounds at the absorption site or cimetidine may induce some change in gastric emptying time and/or motility which caused a slowing of the rate at which clarithromycin reached the absorption site. These hypotheses, if true, could ultimately result in the changes evidenced by this study.

The implications of these results may be far reaching. Cimetidine is a billion dollar drug on the international market and is commonly used for a variety of gastrointestinal ailments including treatment regimens for $H.\text{pylori}$ infection. More recently, cimetidine has found a wide market appeal as a nonprescription remedy for dyspepsia. With clarithromycin now being one of the most commonly prescribed oral antibiotics for community-acquired respiratory infections, the potential for concurrent use is very high. One of the main advantages of clarithromycin over older macrolides, like erythromycin, is its increased spectrum of activity which includes key gram-negative, community-acquired respiratory pathogens like $H.\text{influenzae}$ (16).

Clarithromycin's activity against $H.\text{influenzae}$ is almost solely due to that of 14OHC (MICs at which 90% of isolates are inhibited, versus 1 mg/liter, respectively) (16). Once absorbed, approximately 25% of the bioavailable clarithromycin is converted to 14OHC (3). This results in peak 14OHC concentrations that approximate the MIC at which 90% of isolates are inhibited for $H.\text{influenzae}$. As a result, anything that decreases the concentrations of 14OHC may adversely affect clarithromycin's activity against $H.\text{influenzae}$. This already occurs naturally due to the normal interindividual variability of any metabolic process. This metabolic variability has translated into $H.\text{influenzae}$ eradication variability in clinical trials (range, 20 to 100% eradication) (1, 4, 6, 12–14, 17).

Numerous investigators have pointed out that the higher concentrations of clarithromycin achieved in serum compared to the concentrations of azithromycin and dirithromycin achieved in serum are sometimes believed to be an advantage (5, 15, 16, 18). Those investigators have linked higher concenten-
trations in serum with a number of hypothetical pharmacodynamic advantages including less resistance development, better bacteremic control, and superior pathogen susceptibility. If these advantages are real, then the results of this study suggest that the coadministration of oral cimetidine with oral clarithromycin may negate them. Additionally, it may make clarithromycin’s already variable activity against H. influenzae negligible. How the decreased concentrations of both clarithromycin and 14OHC in serum translate into changes in the concentrations in tissue or at the infection site was beyond the scope of this trial and is worth investigating in the future.

In conclusion, the study suggests that the coadministration of clarithromycin and cimetidine has a negative impact on the pharmacokinetics of clarithromycin. Studies to investigate how this interaction may affect clarithromycin’s activity should be done in the future.

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