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Comparison of the abilities of grepafloxacin and clarithromycin to eradicate potential bacterial pathogens from the sputa of patients with chronic bronchitis: influence of pharmacokinetic and pharmacodynamic variables

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A randomized open-label study was conducted to compare the pharmacokinetics and pharmacodynamics of grepafloxacin with those of clarithromycin in patients with chronic bronchitis whose sputa were colonized with potential bacterial pathogens. Patients received oral grepafloxacin 400 mg od for 10 days (n = 15) or oral clarithromycin 500 mg bd for 10 days (n = 10). Sputum samples were collected before the first dose, 1, 4 and 8 h after a dose on day 1 and then before a dose on days 2, 3, 5, 7 and 10 to determine the time to eradication (T_{erad}) of the potential bacterial pathogens. Blood samples for measurement of grepafloxacin or clarithromycin and 14-hydroxyclarithromycin concentrations were obtained before a dose and 1, 2, 4, 8 and 12 h after doses on days 1 and 5. The area under the inhibitory serum concentration–time curve over 24 h ($AUIC_{24}$), peak serum concentration:MIC ratio (C_{max}:MIC) and the percentage of the dosing interval during which the serum concentration exceeded the MIC (%τ >MIC) were calculated and serum inhibitory titres (SITs) were determined. *Haemophilus* spp. were the predominant potential bacterial pathogens and were recovered from the sputa of 24 patients. Strains of *Streptococcus pneumoniae* were isolated from two patients in the grepafloxacin group and a strain of *Moraxella catarrhalis* was isolated from one patient in the clarithromycin group. *Haemophilus* spp. isolates were eradicated from the sputa of 13 of 14 (93%) patients given grepafloxacin, but from only two of 10 (20%) patients given clarithromycin (P < 0.05). In the other eight (80%) patients who received clarithromycin, the sputum cultures remained positive throughout the 10 day course. Grepafloxacin eliminated potential bacterial pathogens more quickly than clarithromycin (median T_{erad} 4 h versus 76 h). The *S. pneumoniae* strains were eradicated by grepafloxacin within 4 h and the single *M. catarrhalis* strain was eradicated by clarithromycin within 1 h. The greater efficacy of grepafloxacin, compared with that of clarithromycin, in terms of the incidence and speed of eradication of the *Haemophilus* spp. isolates, was associated with higher median values of $AUIC_{24}$ (169 SIT^{-1}·h versus 8.1 SIT^{-1}·h), C_{max}:MIC ratio (23.6 versus 0.7) and %τ >MIC (100% versus 0%). A Hill-type model adequately described the relationship between the percentage probability of eradicating potential bacterial pathogens from sputa and the plasma grepafloxacin concentration.

Introduction

Chronic bronchitis is the fourth leading cause of death in the USA and afflicts approximately 5% of the middle-aged to elderly population.[1,2] It is defined clinically as the daily production of sputum for at least three consecutive months during two consecutive years.[3] Acute exacerbations of chronic bronchitis are among the most common illnesses

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treated by physicians[4] and acute bacterial exacerbations of chronic bronchitis (ABECB) account for up to 67% of all exacerbations,[5–7] the most common pathogens being *Haemophilus* spp., *Streptococcus pneumoniae* and *Moraxella catarrhalis*.[8,9]

Empirical antibiotic therapy is often recommended for patients with ABECB in the primary care and outpatient settings.[10–12] However, the increasing incidences of resistance among the bacterial pathogens commonly associated with respiratory tract infections have become a major concern. A recent multicentre study in the USA revealed that 33% of *Haemophilus influenzae* isolates and almost 93% of *M. catarrhalis* isolates produced β-lactamases[13] and it has been estimated that up to 50% of *H. influenzae* isolates will produce β-lactamases by the year 2000.[14] One study showed that 34% of *S. pneumoniae* isolates exhibited reduced susceptibility to penicillin, with 18% showing high-level resistance.[13]

Pharmacokinetic and pharmacodynamic variables may help in the selection of optimal antibiotics for therapy and, indeed, the relationships among the area under the serum concentration–time curves (AUC), the peak serum concentrations (C_{max}), the MICs and the bactericidal activities of various classes of antimicrobial agents have been extensively investigated. Independent variables that relate pharmacokinetic variables to the pharmacodynamic interaction (i.e. the MIC) include the area under the inhibitory serum concentration–time curve over 24 h of dosing ($AUIC_{24}$), i.e. the area under the serum concentration–time curve over 24 h/MIC (AUC_{24}/MIC), the C_{max}:MIC ratio and the percentage of a dosing interval during which the serum concentration exceeds the MIC (%τ >MIC).[15,16] The $AUIC_{24}$ has been proposed as a useful variable for predicting the efficacies of antimicrobials, such as the aminoglycosides and fluoroquinolones, that exhibit concen tration-dependent killing.[16] For example, for ciprofloxacin, a threshold $AUIC_{24}$ of 125 SIT^{-1}·h has been suggested as being necessary to achieve an optimal outcome in patients with nosocomial pneumonias[17] and C_{max}:MIC ratios >8 have been shown to be necessary to prevent the selection of fluoroquinolone-resistant organisms.[18–20] With regard to macrolide antibiotics, the %τ >MIC has been demonstrated to be the variable most closely associated with a favourable response to treatment with erythromycin and clarithromycin in a mouse model, whereas the $AUIC_{24}$ was the variable most closely associated with the efficacy of azithromycin.[21]

Grepafloxacin is a broad-spectrum fluoroquinolone with *in vitro* activity against both Gram-positive and -negative bacteria.[22] It is more active than first-generation quinolones against *S. pneumoniae* and more active than amoxycillin against *H. influenzae* and *M. catarrhalis*.[22–24] Because of its long half-life and large apparent volume of distribution, grepafloxacin can be administered once daily.[25]

Clarithromycin is an extended-spectrum macrolide which is active *in vitro* against Gram-positive and -negative bacteria, as well as *Mycoplasma, Chlamydia* and *Mycobacterium* spp.[26] In contrast to other macrolides, clarithromycin undergoes first-pass metabolism which produces an active metabolite, 14-hydroxyclarithromycin.[27] The pharmacokinetic profile of clarithromycin is superior to that of erythromycin, thereby allowing twice-daily dosing.

The aim of this study was to test a novel patient model designed to investigate the relationships among antibiotic pharmacokinetics, MICs and rates and speed of eradication of potential bacterial pathogens from the sputa of patients with chronic bronchitis. Grepafloxacin and clarithromycin were chosen as both are licensed for use in the treatment of patients with respiratory tract infections, including ABECB.

Materials and methods

Study population

Patients with chronic bronchitis between 18 and 55 years of age were eligible to be enrolled in the study. In order to be included, they were required to be producing sputum, a Gram's stain of which confirmed the absence of contaminating oropharyngeal squamous epithelial cells and the presence of large numbers of morphologically distinct bacteria. In addition, culture of at least two baseline sputum samples must have yielded one or more of the three pathogens commonly associated with ABECB—*Haemophilus* spp., *M. catarrhalis* and *S. pneumoniae*. Patients experiencing ABECB were excluded, as were those with cystic fibrosis, hepatic diseases, moderate-to-severe renal impairment, severe respiratory tract infections requiring parenteral therapy, gastrointestinal tract diseases which could affect absorption of the study drugs, or human immunodeficiency virus infection or who were terminally ill or immunocompromised. Other exclusion criteria included a history of allergy to fluoroquinolone or macrolide antibiotics and concomitant therapy with other antimicrobials (apart from topical or antifungal agents), theophylline, warfarin, carbamazepine, sucralfate, antacids, iron products (including vitamins) and prednisolone (dosages >10 mg) or steroid equivalents. Patients were excluded if they had received other antimicrobial agents during the 7 days preceding entry into the study or any investigational drug during the 4 weeks preceding entry. Women of childbearing potential were required to have undergone pregnancy tests that yielded negative results and to have used adequate contraception both during and for 1 month after discontinuing a study antibiotic. Female patients were excluded if they were pregnant or lactating.

The study took place at the Clinical Research Center (CRC) of the Clinical Pharmacokinetics Laboratory, Millard Fillmore Hospital/Kaleida Health, Buffalo, NY, USA. It was approved by the Human Research Committee and conducted in accordance with the Declaration of

Helsinki. All patients were informed of the purpose of the study and gave written consent before enrolment.

Study design

This was a randomized open-label study. At least 72 h before receiving the first dose of one of the study drugs, patients reported to the CRC where the following preliminary procedures were undertaken: a history and physical examination, including measurement of vital signs; routine biochemical and haematological investigations and urinalysis; a pregnancy test in women of childbearing potential; and a Gram's stain and culture of a further sputum sample. Patients whose sputa yielded one or more of the three principal pathogens associated with ABECB were allowed to continue in the study, provided that $>10^5$ bacteria (i.e. the presence of more than five bacteria per high power field in a minimum of five fields) were identified on a uniformly distributed Gram's stain.

On the first day of the study the subjects were randomized to receive either oral grepafloxacin 400 mg od or oral clarithromycin 500 mg bd for 10 days. The grepafloxacin dose and the morning clarithromycin dose were administered at the CRC on days 1, 2, 3, 5, 7 and 10; the remaining doses were taken on an out-patient basis. Compliance with the medication taken as an out-patient was assessed with a dosing diary and was considered acceptable if no more than two doses were missed.

Bacteriological assessment

Samples of sputum were obtained just before the first dose and 1, 4 and 8 h after a dose on day 1 and then just before a dose on days 2, 3, 5, 7 and 10. Samples were also collected on the morning of day 14 when patients returned to the CRC for the final assessment. All sputum samples were immediately transported to the laboratory where they were examined macroscopically and the colour and viscosity noted. The samples were Gram-stained and examined microscopically. The morphologies and Gram's stain reactions of the various types of bacteria and the numbers of squamous epithelial cells and polymorphonuclear leucocytes per low power field were recorded. The specimens were cultured and isolates of *Haemophilus* spp., *M. catarrhalis* and *S. pneumoniae* were identified according to standard laboratory procedures. The MICs of grepafloxacin, clarithromycin, erythromycin, penicillin, levofloxacin, ciprofloxacin, azithromycin and trovafloxacin for these isolates were determined by the Etest method (AB Biodisk, Solna, Sweden). The MICs of 14-hydroxyclarithromycin were determined in duplicate by an agar dilution method with Mueller–Hinton agar; the inoculum was 10^5 cfu/spot. The MIC was defined as the lowest concentration yielding no visible growth after incubation at 35°C for 18 h.

Bacteriological response was assessed according to whether or not a potential bacterial pathogen was eradicated and the time to eradication (T_{erad}) following initiation of a course of a study drug. T_{erad} was defined as the time to the first negative sputum culture, provided that subsequent cultures also remained negative. If a potential bacterial pathogen was persistently isolated from sputum specimens, a patient was classified as a bacteriological failure.

Pharmacokinetics and inhibitory titre sampling

On days 1 and 5, samples of blood were obtained just before a dose and 1, 2, 4, 8 and 12 h after a dose. Sputum samples were also collected before a dose and 1, 4 and 8 h after a dose on day 1 and before a dose on the other study days.

Inhibitory titre analysis

The serum inhibitory titres (SITs) for the initial isolate(s) from each patient were determined from blood samples obtained on days 1 and 5. Serum ultrafiltrates were used for the determinations which were carried out according to a modification of a microbroth dilution method recommended by the National Committee for Clinical Laboratory Standards (NCCLS).[28] The ultrafiltrates were obtained by centrifugation of serum samples at 25ºC for 30 min at 1000**g** through a Centrifree micropartition YMT ultrafiltration filter (Amicon Inc., Beverly, MA, USA). The SIT was defined as the highest dilution of the ultrafiltrate (range of dilutions 1:2 to 1:512) which permitted no visible growth; when there was no inhibition, the SIT was taken as 0.

Pharmacokinetic analyses

Grepafloxacin plasma concentrations were measured by a reversed phase, high-performance liquid chromatographic (HPLC) assay. The following instruments were used for the assay: a model 510 pump (Waters Corp., Milford, MA, USA); a model 717 plus autosampler (Waters Corp.); a model 980 fluorescence detector (ABI Division of Perkin–Elmer, Norwalk, CT, USA); a model TCM column heater (Waters Corp.); and a model 746 integrator (Waters Corp.). The prepared samples were chromatographed over a Zorbax Rx C_8 HPLC column (Hewlett Packard, Wilmington, DE, USA). The mobile phase comprised acetonitrile, methanol, 0.1 M citric acid and 0.5 M tetrabutyl ammonium hydroxide in a ratio of 11:22:67:0.5. Linearity was observed over the calibration curve range 0.025–10 mg/L. The overall precision (percentage relative standard deviation, % RSD) and accuracy (percentage analytical recovery, % AR) of the assay were determined from the plasma quality control samples which were analysed at the same time as the study samples and were calculated to be 3.13% and 100%, respectively.

The clarithromycin and 14-hydroxyclarithromycin plasma concentrations were measured by an HPLC assay with the following equipment: a model 510 pump and model 680 gradient controller and solvent select valve (Waters Corp.); a model 8875 fixed volume autosampler (Spectra Physics, San Jose, CA, USA); a Coulochem II electrochemical detector (ESA, Bedford, MA, USA); a Macintosh 7100 computer (Apple Computers Inc., Cupertino, CA, USA); and the Dynamax HPLC data management system (Rainin, Woburn, MA, USA). Linearity was observed over the calibration curve range 0.2–10 mg/L for clarithromycin and 0.18–4.42 mg/L for 14-hydroxyclarithromycin. The % RSD and % AR of the assay were determined from the quality control samples analysed at the same time as the study samples and were calculated to be 1.9 and 101%, respectively, for clarithromycin; the values for 14-hydroxyclarithromycin were similar.

The actual sampling times recorded during the study were used in the data analyses. Pharmacokinetic variables, which were determined from the plasma concentration–time profiles, included the C_{max} and the $\%\tau >$MIC. The AUC for grepafloxacin from time 0 to the last quantifiable concentration (AUC_{0-t}) was calculated with the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.[29] The AUC_{24} for clarithromycin was calculated with the trapezoidal rule from 0 to 12 h to obtain the AUC_{0-12}, then multiplying this value by two in order to obtain the AUC_{0-24}. Variables relating the pharmacokinetic and pharmacodynamic variables of grepafloxacin and clarithromycin included the $AUIC_{24}$, the C_{max}:MIC ratio and the $\%\tau >$MIC. The $AUIC_{24}$ was predicted from the AUC_{24} determined on the day of eradication of a potential bacterial pathogen divided by the MIC for that bacterium. In the event that a potential bacterial pathogen was not eradicated, the AUC_{24} determined at steady-state was used. The $\%\tau >$MIC was calculated by linear interpolation.

Pharmacokinetic and pharmacodynamic modelling

The pharmacokinetic variables for individual patients in each of the antibiotic groups were calculated with a maximum a posteriori probability (MAP) Bayesian fitting procedure.[30,31] Data for the initial estimates of the grepafloxacin pharmacokinetics were obtained by an analysis previously described by Forrest *et al.*[32] which characterized the population pharmacokinetics and pharmacodynamics of oral grepafloxacin in patients with ABECB. A two-compartment linear disposition model with Michaelis–Menten elimination was used to describe the pharmacokinetics of oral grepafloxacin. Data for the initial estimates of clarithromycin and 14-hydroxyclarithromycin pharmacokinetics were obtained according to the methodology used by Amsden *et al.*[33] in a study in which the pharmacokinetics of clarithromycin in healthy volunteers were determined. The pharmacokinetics of clarithromycin and 14-hydroxyclarithromycin were characterized by a two-compartment model. Model discrimination was achieved with the general information criterion and residual analysis.

The relationship between plasma drug concentrations and the probability of eradicating potential bacterial pathogens was investigated by determining the SITs. Similar to the previous pharmacodynamic model of antimicrobial response,[31] the model developed in this study used the MIC midpoint (MIC_{mp}) which was considered the 'true' MIC, i.e. the MIC falling between the reported MIC and the next lower value in the dilution series. MIC_{mp} was computed as the reported MIC multiplied by 0.75. The Hill-type model was developed as follows:

$$\text{Percentage probability of bacterial eradication} = \frac{100 \times C^{H}}{(SIT_{50} \times MIC_{mp})^{H} + C^{H}}$$

where C is the plasma drug concentration, H is Hill's constant and SIT_{50} is the fitted serum inhibitory titre associated with a 50% probability of bacterial eradication. In this model, the product of SIT_{50} and MIC_{mp} was taken as the plasma drug concentration at which the percentage probability of bacterial eradication is 50% (EC_{50}). The estimated variables were H and SIT_{50}. The probability of eradicating a potential bacterial pathogen at baseline (E_o) and the maximum probability of eradicating a potential bacterial pathogen (E_{max}) were assumed to be 0% and 100%, respectively. The ADAPT II package[34] was used for all data modelling.

Statistical analysis

Differences between the antibiotic regimens in terms of bacterial eradication were analysed by Fisher's exact test, statistical significance being defined as $P < 0.05$. The statistical analysis was performed with the SYSTAT for Windows software version 7.0 (SPSS Inc., Chicago, IL, USA).

Results

Patients

Twenty-five patients (15 of whom received grepafloxacin and 10 of whom received clarithromycin) were enrolled in the study; all patients completed the various investigations. Table I summarizes the demographic characteristics of the two groups and the potential bacterial pathogens isolated at entry; there were no statistically significant differences between the groups in terms of these variables. *Haemophilus* spp. were the predominant isolates and were recovered as the sole potential bacterial pathogens from the sputa of 22 patients. Strains of *S. pneumoniae* (in one case with a *Haemophilus* sp. strain) were isolated from only two patients, both of whom were in the grepafloxacin group, and a strain of *M. catarrhalis*, together with a *Haemophilus*

Table I. Demographic characteristics and potential bacterial pathogens isolated from the sputa of the 25 patients enrolled in the study

Characteristic	Antibiotic regimen	
	grepafloxacin (n = 15)	clarithromycin (n = 10)
Gender (male/female)	6/9	4/6
Mean (±S.D.) age (years)	42.5 ± 5.9	38.5 ± 9.3
Mean (±S.D.) weight (kg)	90.6 ± 32.8	93.7 ± 27.5
Potential bacterial pathogen		
Haemophilus spp.	14	10
S. pneumoniae	2	0
M. catarrhalis	0	1

sp. strain, were isolated from one patient in the clarithromycin group. According to the diaries, only one dose of a study drug was missed and no subject was excluded from the analyses on the grounds of poor compliance.

Microbiological outcomes

Haemophilus spp. isolates were eradicated from the sputa of 13 of 14 (93%) patients who received grepafloxacin, with a median T_{erad} after dosing of 4 h. In contrast, *Haemophilus* spp. isolates were eradicated from the sputa of only two of 10 (20%) patients given clarithromycin, the median T_{erad} after dosing being 76 h. The difference between the antibiotic regimens in terms of the incidence of bacterial eradication was statistically significant. *S. pneumoniae* strains were eradicated from the sputa of two grepafloxacin-treated patients within 4 h and the *M. catarrhalis* strain was eradicated from one patient in the clarithromycin group within 1 h.

As shown in Figure 1, the *Haemophilus* spp. isolates were rapidly eradicated from the sputa of patients who received grepafloxacin, the sputum samples from 11 of 14 (79%) patients yielding negative cultures after the first day of antibiotic administration; by day 7, the potential bacterial pathogens had been eradicated from the sputa of 13 of 14 (93%) subjects. In the remaining patient whose sputum was colonized with a *Haemophilus* sp. strain, the bacterium persisted throughout the 14 day monitoring period. On the other hand, the *Haemophilus* spp. isolates were eradicated only slowly from the sputa of patients who received clarithromycin. After 7 days, eradication had been achieved in only two of 10 (20%) patients and, in the remaining eight (80%), the bacteria were isolated repeatedly throughout the 14 day monitoring period.

Bactericidal titres

Table II summarizes the median (range) SITs of grepafloxacin and clarithromycin for the *Haemophilus* spp. isolates. The values for each drug were fairly constant between days 1 and 5, but there were marked differences between the drugs in terms of these values. The median peak SIT for grepafloxacin was 64, while that for clarithromycin was 2. Most of the SITs in the latter group were 0, which is consistent with bacterial growth at all dilutions.

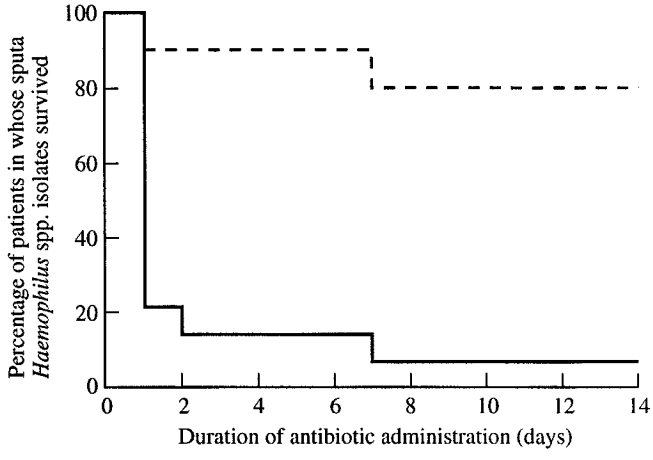

Figure 1. Number of days of antibiotic administration to eradication of *Haemophilus* spp. isolates from sputum (——, grepafloxacin; – – –, clarithromycin).

Pharmacokinetics

Table III shows the MICs, AUC_{24}s, $AUIC_{24}$s, C_{max} values, C_{max}:MIC ratios and %τ >MIC values for grepafloxacin, clarithromycin and 14-hydroxyclarithromycin. The greater efficacy of grepafloxacin, compared with that of clarithromycin, in terms of the extent and speed of eradication of the *Haemophilus* spp. isolates, was associated with a higher median $AUIC_{24}$ (169 SIT^{-1}·h versus 8.1 SIT^{-1}·h), a higher median C_{max}:MIC ratio (23.6 versus 0.7) and a higher median %τ >MIC (100% versus 0%).

Table II. SITs for *Haemophilus* spp. isolates

Day	Time (h) after dosing	Median (range) SITs[a]	
		grepafloxacin	clarithromycin
1	before dose	0 (0–4)	0 (0–2)
	1	64 (4–256)	0 (0–4)
	2	64 (8–512)	1 (0–4)
	4	32 (4–512)	2 (0–4)
	8	32 (8–128)	0 (0–2)
	12	16 (4–128)	0 (0–2)
5	before dose	16 (2–64)	1 (0–2)
	1	48 (8–256)	0 (0–2)
	2	64 (16–256)	2 (0–2)
	4	64 (4–256)	1 (0–4)
	8	32 (0–128)	0 (0–2)
	12	32 (2–128)	0 (0–2)

[a]Results are expressed as the reciprocals of the SITs.

Table III. Median (range) pharmacokinetic and pharmacodynamic variables for grepafloxacin, clarithromycin and 14-hydroxyclarithromycin

Variable	Grepafloxacin	Clarithromycin	14-Hydroxyclarithromycin
MIC (mg/L) for isolates of *Haemophilus* spp.	0.06 (0.008–0.125)	6 (1–8)	3 (0.5–4)
AUC_{24} (mg·h/L)	10.4 (7.4–13.2)	49.4 (15.2–75.8)	14.6 (8.2–32.4)
$AUIC_{24}$ (SIT^{-1}·h)	169 (71–1103)	8.1 (1.4–46)	5 (2.1–42)
C_{max} (mg/L)	1.1 (0.8–1.9)	3.9 (0.7–5.1)	0.9 (0.5–1.9)
C_{max}:MIC ratio	23.6 (8–145)	0.7 (0.1–3.8)	0.4 (0.1–2.5)
$\%\tau > MIC$	99.8 (99.2–100)	0 (0–72.5)	0 (0–96.7)

Pharmacokinetic/pharmacodynamic model

The use of a two-compartment model with Michaelis–Menten elimination yielded an excellent correlation between the observed and fitted grepafloxacin concentrations ($r^2 = 0.936$). Similarly, co-modelling of the plasma clarithromycin and 14-hydroxyclarithromycin concentrations showed a high degree of model precision, as demonstrated by the high correlation between the observed and fitted concentrations of the two drugs ($r^2 = 0.968$ and 0.87, respectively).

A Hill-type model which related the percentage probability of eradication of a potential bacterial pathogen and the plasma grepafloxacin concentration was fitted for each patient. The percentage probability of potential bacterial pathogen eradication was accurately predicted in approximately 95% of observations. As illustrated in Figure 2, the individual plots of the Hill-type model approached a step-function, with a median Hill's constant of 3.9 (range 1.9–10.6). The EC_{50}s were low and varied from patient to

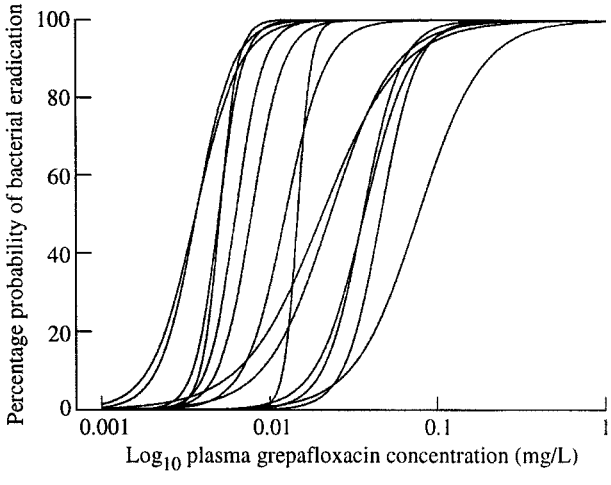

Figure 2. Individual plots ($n = 14$) of the Hill-type model showing the relationship between plasma grepafloxacin concentration and the percentage probability of eradicating *Haemophilus* spp. isolates from sputum.

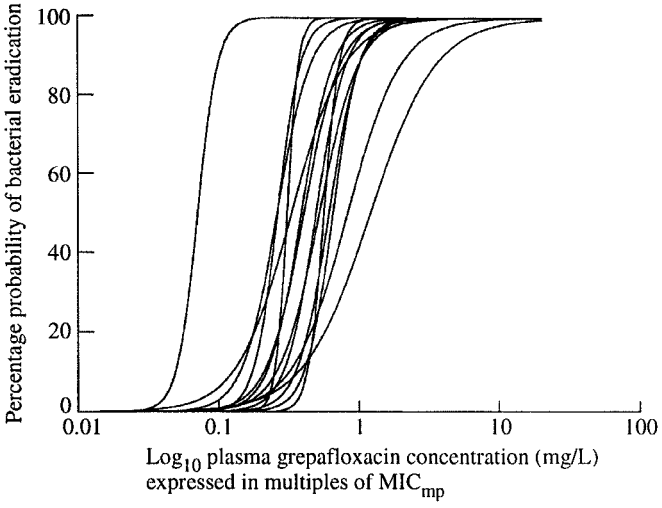

Figure 3. Individual plots (n = 14) of the Hill-type model showing the relationship between plasma grepafloxacin concentration corrected for MIC_{mp} and the percentage probability of eradicating *Haemophilus* spp. isolates from sputum.

patient, the median being 0.014 mg/L (range 0.0036–0.077 mg/L). When the plasma grepafloxacin concentrations were corrected for the MICs, less variability in the EC_{50}s was observed (Figure 3), the median (range) EC_{50} now being 0.45 (0.07–1.2) of the MIC_{mp}.

As most of the SITs in patients in the clarithromycin group were 0 (i.e. there was no growth inhibition at any serum dilution), pharmacokinetic/pharmacodynamic modelling for clarithromycin was not performed.

Discussion

Chronic bronchitis was selected as the underlying disease in this study because the condition is sufficiently common and because there are relatively large numbers of patients with persistently positive sputum cultures, making it easier to recruit patients to the study. The patients were from western New York and were suffering with chronic bronchitis, but were not experiencing acute exacerbations at the time. As the patients were not acutely ill, they were presumably chronically infected or colonized. It was not the intention of the study to produce long-term changes in the disease state with short courses of antibiotics.

The objective of giving antibiotics to patients with ABECB is, at least in part, to eradicate the pathogens from the sputum. In the present study, the bacteriological success rate in patients receiving oral grepafloxacin 400 mg od was significantly higher than that in patients given oral clarithromycin 500 mg bd. Eradication of *Haemophilus* spp. strains was achieved in 13 of 14 (93%) patients who received grepafloxacin and was sustained throughout the duration of the study. In contrast, *Haemophilus* spp. strains were eradicated from the sputa of only two of 10 (20%) patients given clarithromycin. Moreover, grepafloxacin eradicated these bacteria more rapidly than clarithromycin (median T_{erad}, 4 h and 76 h, respectively). In the eight clarithromycin-treated patients in whom eradication was not achieved, sputum cultures yielded potential bacterial pathogens throughout the 10 day course and at the follow-up examination 4 days after administration of the last dose.

Bacterial eradication can be predicted on the basis of an optimal relationship between the pharmacokinetics of fluoroquinolones and the MICs for the pathogens. In a previous study involving patients with nosocomial lower respiratory tract infections, the optimal $AUIC_{24}$ for ciprofloxacin was 125 $SIT^{-1}\cdot h$.[17] When the $AUIC_{24}$ fell below this threshold, the microbiological failure rate was approximately 70%. The response rate associated with grepafloxacin has also been shown to be highly related to the $AUIC_{24}$ in a study of patients with ABECB.[31] A probability of bacteriological cure of 90% was associated with an $AUIC_{24}$ of >69 $SIT^{-1}\cdot h$ and a probability of clinical cure of 98% was associated with an $AUIC_{24}$ of >175 $SIT^{-1}\cdot h$. In our study, the $AUIC_{24}$s for the patients in the grepafloxacin group were ⩾71 $SIT^{-1}\cdot h$ and *Haemophilus* spp. strains were eradicated from the sputa of 13 of the 14 patients colonized with these organisms. However, a correlation between the $AUIC_{24}$ and T_{erad} was not detected, presumably because all of the bacterial strains were eradicated equally rapidly.

Successful eradication of *Haemophilus* spp. strains from the sputa of patients with chronic bronchitis who received oral grepafloxacin 400 mg od was associated with high $AUIC_{24}$s, C_{max}:MIC ratios and $\%\tau$ >MIC values. These high values might have been accounted for, at least in part, by the low MICs of grepafloxacin for the *Haemophilus* spp. isolates (median, 0.06 mg/L; range, 0.008–0.125 mg/L). A high C_{max}:MIC ratio should be beneficial to patients with ABECB as it has been shown to be necessary to prevent the selection of resistant strains.[16] Previous computer simulations indicated that the likelihood of bacteriological cure would be increased if the AUC exceeded the MIC for at least 80% of the interval between doses.[15] In this study, the plasma grepafloxacin concentrations in all patients remained above the MICs for most of a 24 h dosing interval, this being associated with a high incidence of eradication of potential bacterial pathogens.

The incidence of eradication of *Haemophilus* spp. strains from the sputa of patients receiving clarithromycin was low. This low incidence was associated with low $AUIC_{24}$s, C_{max}:MIC ratios and $\%\tau$ >MIC values as the correlations among these variables were high. Although the median AUC_{24} and C_{max} for clarithromycin were four- to five-fold greater than those for grepafloxacin, the median MICs of clarithromycin and 14-hydroxyclarithromycin were almost 100-fold greater than that of grepafloxacin, thereby resulting in a lower median $AUIC_{24}$, C_{max}:MIC ratio and $\%\tau$ >MIC. It has been suggested that the $\%\tau$ >MIC is the

variable that most reliably predicts the efficacy of clarithromycin.[21] In this study, the concentrations of clarithromycin in the plasma of the seven patients from whose sputa *Haemophilus* spp. isolates were not eradicated remained below the MICs for these bacteria throughout the 12 h dosing interval. In one patient in whom a *Haemophilus* sp. strain was eradicated, the $\%\tau > MIC$ was approximately 73%. It is interesting to note that the rapid eradication of an *M. catarrhalis* strain from the sputum of a patient who received clarithromycin was associated with an $AUIC_{24}$ of 1112 $SIT^{-1}\cdot h$, a C_{max}:MIC ratio of 104 and a $\%\tau > MIC$ of 99.8%.

In vitro, 14-hydroxyclarithromycin is more potent against *Haemophilus* spp. than clarithromycin which has only modest activity.[26] The activity of clarithromycin is enhanced by its active metabolite.[35] Our study, however, showed that 14-hydroxyclarithromycin does not enhance the efficacy of clarithromycin in terms of eradicating strains of *Haemophilus* spp. from sputa. The median $AUIC_{24}$ and C_{max}:MIC ratio for clarithromycin were almost twice those for its metabolite.

On the basis of the SITs, a Hill-type model adequately described the relationship between the probability of bacterial eradication and the plasma grepafloxacin concentration. As suggested from the Hill-type plots, which showed a step-function, a minor change in the plasma grepafloxacin concentration would markedly increase the probability of eradicating *Haemophilus* spp. isolates from sputa. As demonstrated in Figure 3, there was considerable patient-to-patient variability in the EC_{50}s, much of which was probably accounted for by variations in the MICs for the isolates.

Failure to achieve a successful clinical outcome with empirical antibiotic therapy in patients with ABECB has been attributed to inadequate activity *in vitro*, resistance to the antibiotics administered, inadequate pharmacokinetic profiles and individual patient factors.[36] Armed with knowledge of the predominant pathogens, the local susceptibility patterns of these organisms, the *in vitro* activities of candidate antibiotics and a patient's age and underlying condition, it should be possible to limit the number of appropriate antibiotics suitable for empirical therapy. For the empirical treatment of patients with ABECB, however, pharmacokinetics should be taken into account when choosing which antibiotic to use. It should be possible to use pharmacokinetic/pharmacodynamic variables such as the $AUIC_{24}$, the C_{max}:MIC ratio and the $\%\tau > MIC$ to predict the efficacies of individual antibiotics. In our study, the high incidence of eradication of potential bacterial pathogens from the sputa of patients with chronic bronchitis who received grepafloxacin was associated with high values of these variables. In contrast, the low incidence of eradication in patients given clarithromycin was associated with low values.

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