Efficacy and Tolerability of Once-Daily Grepafloxacin Compared with Clarithromycin in the Treatment of Acute Bacterial Exacerbations of Chronic Bronchitis

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Abstract

Objectives: The clinical and bacteriological efficacies and tolerability of grepafloxacin 400mg once daily for 10 days were compared with clarithromycin 500mg twice daily for 10 days in patients with acute bacterial exacerbations of chronic bronchitis (ABECB).

Patients and Study Design: 379 patients with signs and symptoms of ABECB were enrolled in a randomised, double-blind clinical trial conducted at 15 outpatient centres in the USA. Eligible patients were randomly assigned to receive either grepafloxacin plus matched clarithromycin placebo (n = 192) or clarithromycin plus matched grepafloxacin placebo (n = 187).

Results: The two treatment groups were equivalent with respect to clinical efficacy, and no statistically significant differences in the incidence of drug-related adverse events were seen between the two groups. A satisfactory clinical outcome was achieved in 88% (130 of 148) and 89% (134 of 150) of clinically evaluable patients treated with grepafloxacin or clarithromycin, respectively. The primary pathogens isolated from pretreatment sputum specimens were *Haemophilus parainfluenzae*, *H. influenzae*, *Moraxella catarrhalis*, *Streptococcus pneumoniae* and *Staphylococcus aureus* (31, 18, 6, 5 and 4% of isolates, respectively). Pathogens were eradicated or presumed to be eradicated in 88% (113 of 129) and 78% (97 of 125) of bacteriologically evaluable patients treated with grepafloxacin or clarithromycin, respectively. Both treatments were associated with a low incidence of drug-related adverse events.

Conclusion: These results indicate that grepafloxacin 400mg once daily for 10 days is as well tolerated and as clinically effective as clarithromycin 500mg twice daily for 10 days in patients with ABECB.

Chronic bronchitis is an obstructive lung disease affecting an estimated 5% of the middle-aged and elderly population in the USA.^[1] Acute bacterial exacerbations of chronic bronchitis (ABECB) occur frequently in affected individuals and are characterised by increased cough and sputum production, dyspnoea and sometimes fever.^[2] *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Moraxella catarrhalis* are major pathogens identified in ABECB.^[3,4] Antimicrobial agents directed against these pathogens play a role in preventing suppurative complications and in reducing the morbidity and mortality associated with acute bacterial infections in patients with chronic pulmonary disease.^[2,5]

Patients with ABECB often receive empirical antibiotic treatment. Empirical therapy with some β -lactam and macrolide antibiotics has been compromised by the rise in incidence of penicillin resistance and β -lactamase production among the common pathogens.^[6-8]

The number of highly penicillin-resistant isolates of *S. pneumoniae* approaches 14% in the USA, while intermediate resistance is seen in 20% or more of strains, reflecting regional variability.^[9] Furthermore, the incidence of *S. pneumoniae* multiresistance is increasing, resulting in decreased susceptibility of these strains to macrolides and some other antibiotics as well.^[9,10] For example, approximately 23% of *S. pneumoniae* clinical isolates are resistant to macrolide antibiotics, and this resistance occurs primarily in strains with high level or intermediate resistance to penicillin (Glaxo Wellcome, data on file). In addition, more than 90% of *M. catarrhalis* clinical isolates and up to 40% of *H. influenzae* strains produce β -lactamases, reducing susceptibility to β -lactam antibiotics.^[11-13] Therefore, new antimicrobial agents that are well tolerated and efficacious are necessary for effective therapy in ABECB.

Grepafloxacin (Glaxo Wellcome) is a broad-spectrum fluoroquinolone with greater activity against Gram-positive bacteria than first-generation quinolones, as well as excellent activity against Gram-negative and atypical organisms.^[14,15]

Grepafloxacin also has demonstrated *in vitro* activity against penicillin-resistant *S. pneumoniae* isolates. The drug is well distributed in respiratory fluids and tissues, and its pharmacokinetic parameters permit once-daily dose administration.^[16,17] A once-daily dosage regimen of grepafloxacin is currently indicated for the treatment of lower respiratory tract infections, including ABECB and community-acquired pneumonia, as well as for some sexually transmitted diseases.

Clarithromycin (Abbott Laboratories) is an extended-spectrum macrolide antibiotic currently approved for use twice daily in the treatment of upper and lower respiratory tract infections including ABECB. Clarithromycin demonstrates good bioavailability and tissue distribution.^[18]

The present study was undertaken to compare the tolerability and efficacy of grepafloxacin 400mg once daily for 10 days with clarithromycin 500mg twice daily for 10 days in the treatment of patients with ABECB.

Patients and Methods

This study (protocol number GFXA4001) was a double-blind, multicentre, randomised clinical trial conducted at 15 outpatient or private practice centres throughout the USA. All patients provided written informed consent prior to entry in the study, and the study protocol was approved by all Institutional Review Boards in accordance with FDA guidelines.

Patient Selection

Male and female outpatients aged 18 years or older were eligible to participate in the study if they had an established diagnosis of chronic bronchitis (defined as the daily production of sputum during 3 consecutive months for greater than 2 successive years) and if the onset of exacerbated symptoms was within 14 days prior to enrolment. Eligible patients displayed signs and symptoms at enrolment compatible with ABECB, consisting of three or more of the following six symptoms: increased frequency and/or severity of cough; increase in sputum volume; purulent changes in sputum; dys-

pnoea or increased dyspnoea; increased chest congestion as indicated by adventitious sounds, and chills and/or fever.

Patients were not eligible if a chest x-ray taken within 48 hours prior to enrolment indicated the presence of pneumonia as evidenced by new localised infiltrate, pleural effusion or consolidation.

Patients were excluded from the study if they presented with a history of hypersensitivity or phototoxicity reaction to any quinolone or macrolide antibiotic. Patients presenting with the following conditions or diseases were excluded from participation in the study: neutropenia, immune deficiency, AIDS, severe uncontrolled diabetes mellitus, significant heart disease, hepatic disease, splenectomy, concomitant respiratory disease, seizure disorders or gastrointestinal disease affecting absorption of antibiotics.

Exclusion criteria also consisted of concomitant therapy with theophylline, warfarin or any oral anticoagulant, systemic corticosteroids, carbamazepine, ketoconazole, digoxin, ergotamine, dihydroergotamine, triazolam, cisapride, astemizole, terfenadine, alfentanil, bromocriptine, cyclosporin, disopyramide, fluconazole, hexobarbital, lovastatin, omeprazole, phenytoin, pimozide, valproic acid and zidovudine. Patients were excluded if they had received any systemic antimicrobial agent within the previous 7 days or had failed prior treatment for the current ABECB. Female subjects were excluded if they were pregnant or lactating or were of childbearing potential and not using approved methods of contraception.

Microbiological Investigations

A sputum specimen for culture was obtained within 48 hours before starting treatment. Sputum specimens were examined by Gram stain, and only specimens containing ≥ 25 polymorphonuclear leucocytes/low power field were considered acceptable. Sputum specimens were shipped to a central laboratory (Covance, Indianapolis, IN) and the infecting organisms were identified and tested for susceptibility to grepafloxacin and clarithro-

mycin (all *S. pneumoniae* isolates were also tested for penicillin susceptibility) via a tube or agar dilution minimum inhibitory concentration determination using breakpoints established by the National Committee for Clinical Laboratory Standards.^[19,20] β -Lactamase production was determined for all *Haemophilus* species and *M. catarrhalis* isolates using a nitrocefin base test.

Antimicrobial Therapy

Eligible patients were randomly assigned to receive either grepafloxacin 400mg once daily (plus matched clarithromycin placebo) or clarithromycin 500mg twice daily (plus matched grepafloxacin placebo) for 10 days. Study medication was administered without regard to meals, although patients were advised to avoid taking medication concurrently with large amounts of caffeine-containing foods or beverages. Products containing iron or zinc, multivitamin preparations, antacids and sucralfate were not to be taken within 2 hours before or 2 hours after taking study medication. Concurrent treatment with these products was discouraged throughout the treatment period. A urine specimen (>10 ml) was obtained 4 to 6 days after the start of treatment and assessed by a biological assay for the presence of antibiotic in order to confirm compliance with therapy.

Clinical and Bacteriological Evaluations

Patients were evaluated for clinical symptoms and physical signs of infection 4 to 6 days after starting treatment (during-treatment visit), 1 to 3 days after treatment (end-of-treatment visit), and 21 to 24 days after treatment (follow-up visit). Clinical assessments were made on the basis of frequency and/or severity of cough, volume of sputum production, qualitative changes in sputum purulence, dyspnoea, chest congestion, and chills and/or fever (oral temperature $\geq 100.0^{\circ}\text{F}$ or $\geq 37.8^{\circ}\text{C}$).

The clinical response at the time of withdrawal or at the follow-up visit for all cases was classified by the investigator as:

- cure (clinical signs and symptoms of ABECB improved or resolved at the 1- to 3-day post-treatment visit and were absent at the 21- to 24-day post-treatment visit);
- improvement (improved but with incomplete resolution of the clinical signs and symptoms of ABECB by the 21- to 24-day post-treatment visit);
- failure (no apparent response to treatment after 3 or more days of therapy, or patient withdrawn because of a study drug-related adverse event);
- recurrence (resolution or improvement of clinical signs and symptoms of ABECB at the 1- to 3-day post-treatment visit with recurrence of clinical symptoms by 21 to 24 days post-treatment).

Study patients were considered clinically unevaluable if they received concomitant treatment with a non-study systemic antimicrobial agent, received less than 3 days of treatment with the study drug, failed to complete all scheduled study visits, showed evidence of poor compliance, withdrew from the study because of a non-study drug-related adverse event, were enrolled in violation of the selection criteria, or deviated significantly from the study protocol in any other way.

Bacteriological response to treatment was defined as:

- cure (initial pathogen eradicated during or at completion of therapy);
- presumed cure (culturable material not available at the during- or post-treatment visits as a result of clinical improvement);
- failure (initial pathogen still present after at least 3 days of therapy without eventual clearance);
- presumed failure (culturable material not available and the patient was discontinued from the study with an unsatisfactory clinical response);
- recurrence (eradication and then reisolation of the initial pathogen);
- cure with colonisation (eradication of initial pathogen plus isolation of at least one new non-pathogen not associated with clinical symptoms);
- cure with superinfection (eradication of initial pathogen plus isolation of one or more new pathogens);
- failure with superinfection (no eradication of initial pathogen plus isolation of one or more new pathogens); or
- failure with resistance [bacteriological failure as defined above with initial pathogen(s) developing resistance to study drugs during the course of therapy].

In cases where more than one organism was isolated from a single sample, each pathogen was evaluated separately. A study patient was considered bacteriologically unevaluable if the patient was clinically unevaluable or if there was inability to culture a pretreatment bacterial pathogen. Patients with negative pretreatment cultures remained in the study for the evaluation of clinical efficacy.

Tolerability Assessment

Blood was collected for haematology and clinical chemistry testing at the enrolment and 1- to 3-day post-treatment visits. No clinical chemistry or haematology testing was performed at the during-treatment or 21- to 24-day post-treatment visits unless abnormalities were noted in the sample collected at the previous visit. At each visit, adverse events determined by spontaneous patient reports and/or nonsuggestive questioning were assessed by investigators for severity, frequency, outcome and potential relationship to study drug.

Statistical Analyses

The primary study end-point was the satisfactory clinical response rate (cure plus improvement) in the clinically evaluable patient population. The trial was designed to test for statistical equivalence between the grepafloxacin and clarithromycin treatment groups. For satisfactory outcomes $\geq 80\%$ and $< 90\%$, treatment equivalence was established if the lower limit of the 95% confidence interval (CI) around the difference in response rates was greater than or equal to -15% and if the confidence interval included the value of zero. A sample size of 300 clinically evaluable patients was adequate

to establish treatment equivalence with the assumption that the observed treatment difference would be no more than 6%.

Secondary end-points were the satisfactory bacteriological outcome (cure, presumed cure and cure with colonisation) in the microbiologically and clinically evaluable population and incidence of adverse events. Other efficacy measures included a subgroup summary of age, gender and race to informally compare the rates of satisfactory clinical response between treatment groups at the follow-up assessment.

A 2-tailed Fisher's exact test was used to compare differences between treatment groups in clinical and bacteriological efficacies and incidences of the most common drug-related adverse events (defined as an incidence of the specified adverse event of 5% or greater in any group). All tests were 2-sided and values less than 0.05 were considered significant.

Results

Three hundred and seventy-nine patients with chronic bronchitis were enrolled in the study, of which 192 were randomised to receive grepafloxacin and 187 were randomised to receive clarithromycin. Demographic characteristics between groups were comparable (table I). Clinical symptoms at enrolment occurred with similar frequency in both treatment groups (table II). Two patients in the clarithromycin group were considered unevaluable since their pretreatment chest radiographs revealed lobar consolidation. Neither lobar infiltrate nor pleural effusion was present in any patient enrolled in the study.

The median dosage duration was 10 days for both treatment groups, while the mean dosage duration was 9.8 and 9.9 days for the grepafloxacin and clarithromycin groups, respectively. Good compliance was seen at the 4- to 6-day during-treatment visit with both treatment regimens; antibiotic activity was detected in the urine of 175 of 192 (91%) and 176 of 187 (94%) patients receiving grepafloxacin or clarithromycin, respectively.

Table I. Summary of demographic characteristics of study patients

	Grepafloxacin (10 days) [n = 192]	Clarithromycin (10 days) [n = 187]
Gender [no. (%)]		
Male	100 (52%)	109 (58%)
Female	92 (48%)	78 (42%)
Ethnic origin [no. (%)]		
Caucasian	138 (72%)	138 (74%)
Black	48 (25%)	44 (24%)
Hispanic	2 (1%)	3 (2%)
Asian	4 (2%)	2 (1%)
Age (y)		
Mean $\pm$ SEM	47.3 $\pm$ 1.1	49.9 $\pm$ 1.1
Range	18.4 - 90.6	18.8 - 85.0
Weight (kg)		
Mean $\pm$ SEM	80.8 $\pm$ 1.4	79.7 $\pm$ 1.4
Range	46.3 - 149.4	44.0 - 164.8

Clinical Outcome

Table III presents the clinical outcome of patients in the two treatment groups. Of the 379 patients enrolled, 298 (79%) were clinically evaluable. Of the 81 clinically unevaluable patients, 27 (7%) were lost to follow-up, 16 (4%) had enrolment violations, 15 (4%) failed to complete study visits, 9 (2%) withdrew either because of a non-study drug-related adverse event or for reasons not related to adverse events, and 14 (4%) had other protocol violations. A satisfactory clinical response (cure or improvement) was obtained in 88 and 89% of clinically evaluable patients treated with grepafloxacin or clarithromycin, respectively, and equivalence was established through 95% CI analysis.

Patients in both treatment groups demonstrated marked improvement at the first during-treatment measurement (4 to 6 days after initiation of therapy), and continued to improve throughout the study, as judged by the reduction in the proportion of patients with clinical symptoms of ABECB, as well as by the substantial decreases in the severity of the symptoms that were present (table II and fig. 1). The incidence of severe productive cough decreased from 29% in both groups at enrolment to 5% in the grepafloxacin group and 3% in the

Table II. Clinical symptoms of patients with acute bacterial exacerbations of chronic bronchitis in the intent-to-treat population at time of enrolment, 4 to 6 days after initiation of treatment (during-treatment visit) and at 1 to 3 days (end-of-treatment visit) and 21 to 24 days (follow-up visit) after treatment

Symptom	Severity	At enrolment		During-treatment visit		End-of-treatment visit		Follow-up visit	
		grepafloxacin 10 days [n = 192]	clarithromycin 10 days [n = 187]	grepafloxacin 10 days [n = 185]	clarithromycin 10 days [n = 181]	grepafloxacin 10 days [n = 171]	clarithromycin 10 days [n = 170]	grepafloxacin 10 days [n = 154]	clarithromycin 10 days [n = 156]
Productive cough	Mild	12 (6%)	11 (6%)	99 (54%)	124 (69%)	119 (70%)	118 (69%)	90 (58%)	84 (54%)
	Moderate	125 (65%)	122 (65%)	61 (33%)	39 (22%)	15 (9%)	4 (2%)	8 (5%)	8 (5%)
	Severe	55 (29%)	54 (29%)	9 (5%)	5 (3%)	2 (1%)	2 (1%)	3 (2%)	2 (1%)
	Total	192 (100%)	187 (100%)	169 (91%)	168 (93%)	136 (80%)	124 (73%)	101 (66%)	94 (60%)
	Absent	0	0	16 (9%)	13 (7%)	35 (20%)	46 (27%)	53 (34%)	62 (40%)
Increased sputum production	Mild	12 (6%)	18 (10%)	111 (60%)	114 (63%)	114 (67%)	106 (62%)	83 (54%)	72 (46%)
	Moderate	149 (77%)	131 (70%)	52 (28%)	38 (21%)	12 (7%)	6 (4%)	9 (6%)	8 (5%)
	Severe	31 (16%)	38 (20%)	7 (4%)	7 (4%)	2 (1%)	2 (1%)	3 (2%)	1 (<1%)
	Total	192 (100%)	187 (100%)	170 (92%)	159 (88%)	128 (75%)	114 (67%)	95 (62%)	81 (52%)
	Absent	0	0	15 (8%)	22 (12%)	43 (25%)	56 (33%)	59 (38%)	75 (48%)
Purulent change in sputum	Mild	18 (9%)	20 (11%)	93 (50%)	102 (56%)	33 (19%)	27 (16%)	20 (13%)	13 (8%)
	Moderate	147 (76%)	132 (71%)	40 (22%)	29 (16%)	4 (2%)	3 (2%)	4 (3%)	6 (4%)
	Severe	24 (13%)	34 (18%)	2 (1%)	1 (<1%)	2 (1%)	1 (<1%)	1 (<1%)	0
	Total	189 (98%)	187 (99%)	135 (73%)	132 (73%)	39 (23%)	31 (18%)	25 (16%)	19 (12%)
	Absent	3 (2%)	1 (<1%)	50 (27%)	49 (27%)	132 (77%)	139 (82%)	129 (84%)	137 (88%)
Dyspnoea	Mild	62 (32%)	72 (39%)	78 (42%)	73 (40%)	38 (22%)	38 (22%)	21 (14%)	24 (15%)
	Moderate	78 (41%)	74 (40%)	28 (15%)	18 (10%)	11 (6%)	8 (5%)	4 (3%)	9 (6%)
	Severe	19 (10%)	16 (9%)	2 (1%)	4 (2%)	0	1 (<1%)	1 (1%)	2 (1%)
	Total	159 (83%)	162 (87%)	108 (58%)	95 (52%)	49 (29%)	47 (28%)	26 (17%)	35 (22%)
	Absent	33 (17%)	25 (13%)	77 (42%)	86 (48%)	122 (71%)	123 (72%)	128 (83%)	121 (78%)
Chest congestion	Mild	33 (17%)	31 (17%)	117 (63%)	118 (65%)	38 (22%)	47 (28%)	21 (14%)	15 (10%)
	Moderate	137 (71%)	132 (71%)	21 (11%)	20 (11%)	5 (3%)	1 (<1%)	5 (3%)	7 (4%)
	Severe	14 (7%)	18 (10%)	2 (1%)	4 (2%)	1 (<1%)	1 (<1%)	2 (1%)	1 (<1%)

Table III. Clinical efficacy of grepafloxacin and clarithromycin in the treatment of patients with acute bacterial exacerbations of chronic bronchitis

Clinical outcome at follow-up	Grepafloxacin (10 days) [no. (%)]	Clarithromycin (10 days) [no. (%)]
Cure (C)	108 (73)	114 (76) ^a
Improvement (I)	22 (15)	20 (13)
Satisfactory (C + I) ^b	130 (88)	134 (89)
Failure (F)	9 (6)	7 (5)
Recurrence (R)	9 (6)	9 (6)
Unsatisfactory (F + R)	18 (12)	16 (11)
Total, evaluable patients	148	150
Unevaluable patients	44	37
Total, all patients	192	187

a Percentage of evaluable patients.

b Comparison of satisfactory outcomes between groups demonstrated equivalence, 95% confidence interval = (-0.09, 0.06); $p = 0.69$.

clarithromycin group at the first during-treatment visit.

Similarly, the percentage of patients with severe increased sputum production decreased from 16% at enrolment to 4% after 4 to 6 days of treatment (first during-treatment visit) in the grepafloxacin group. Similar rates of symptom improvement were observed in the clarithromycin group.

When clinical efficacy was analysed by organism for the five primary pathogens (*H. parainfluenzae*, *H. influenzae*, *S. pneumoniae*, *M. catarrhalis* and *Staphylococcus aureus*) isolated from patients enrolled in the trial, satisfactory clinical response rates for grepafloxacin were comparable with those for clarithromycin (table IV).

Bacteriological Outcome

Bacterial isolates were obtained from the pre-treatment sputum specimens of 330 of 379 (87%) study patients, and 254 (67%) of the 379 patients enrolled were bacteriologically evaluable. The primary pathogens isolated were *H. parainfluenzae* (31% of isolates), *H. influenzae* (18%), *M. catarrhalis* (6%), *S. pneumoniae* (5%) and *S. aureus* (4%). 19% of the *H. influenzae* isolates and 94% of the *M. catarrhalis* isolates tested for

Fever	Total	184 (96%)	181 (97%)	140 (76%)	142 (78%)	44 (26%)	49 (29%)	28 (18%)	23 (15%)
	Absent	8 (4%)	6 (3%)	45 (24%)	39 (22%)	127 (74%)	121 (71%)	126 (82%)	133 (85%)
	Mild	9 (5%)	7 (4%)	3 (2%)	0	2 (1%)	0	1 (<1%)	1 (<1%)
	Moderate	6 (3%)	3 (2%)	0	0	0	0	0	1 (<1%)
	Severe	0	0	0	0	0	0	0	0
	Total	15 (8%)	10 (5%)	3 (2%)	0	2 (1%)	0	1 (<1%)	2 (1%)
	Absent	177 (92%)	177 (95%)	182 (98%)	181 (100%)	169 (99%)	170 (100%)	153 (>99%)	154 (99%)
	Mild	51 (27%)	43 (23%)	16 (9%)	12 (7%)	5 (3%)	5 (3%)	2 (1%)	2 (1%)
	Moderate	15 (8%)	11 (6%)	1 (<1%)	1 (<1%)	0	2 (1%)	0	2 (1%)
	Severe	2 (1%)	2 (1%)	1 (<1%)	1 (<1%)	0	0	0	1 (<1%)
Chills	Total	68 (36%)	56 (30%)	18 (10%)	14 (8%)	5 (3%)	7 (4%)	2 (1%)	5 (3%)
	Absent	124 (64%)	131 (70%)	167 (90%)	167 (92%)	166 (97%)	163 (96%)	152 (99%)	151 (97%)

Fig. 1. Severity of symptoms in clinically evaluable patients with acute bacterial exacerbations of chronic bronchitis in the grepafloxacin (G) or clarithromycin (C) group at the time of enrolment, at the 4- to 6-day during-treatment visit, and at the 21- to 24-day post-treatment follow-up visit.

β -lactamase production were positive. Of the 354 pathogens isolated from the 330 patients, greater than 99% were susceptible to grepafloxacin, while 81% were susceptible to clarithromycin (table V).

Eight of the 28 (29%) *S. pneumoniae* isolates demonstrated resistance to penicillin, with five of

these eight (63%) showing intermediate resistance and the remaining three (37%) being highly resistant to penicillin. All *S. pneumoniae* isolates demonstrated susceptibility to grepafloxacin, while five of the 28 (18%) isolates were highly resistant to clarithromycin.

Table IV. Clinical efficacy of grepafloxacin and clarithromycin analysed by organism in evaluable patients at follow-up

Organism	Satisfactory clinical outcome ^a	
	grepafloxacin (10 days) [no. (%)]	clarithromycin (10 days) [no. (%)]
<i>Streptococcus pneumoniae</i>	6/7 (86)	7/7 (100)
<i>Haemophilus parainfluenzae</i>	67/75 (89)	65/71 (92)
<i>H. influenzae</i>	31/33 (94)	28/32 (88)
<i>Moraxella catarrhalis</i>	13/13 (100)	9/10 (90)
<i>Staphylococcus aureus</i>	8/10 (80)	8/9 (89)

a Satisfactory clinical outcome includes clinical cure and clinical improvement.

When bacteriological outcomes were analysed by organism, satisfactory responses were seen in 86% (6/7) and 83% (5/6) of *S. pneumoniae* isolates in the grepafloxacin and clarithromycin groups, respectively. Satisfactory outcomes for *H. para-*

influenzae were 87% (65/75) versus 83% (59/71) for the grepafloxacin and clarithromycin groups, respectively. For *H. influenzae*, *M. catarrhalis* and *S. aureus* satisfactory responses reported were 91% (30/33) versus 75% (24/32), 100% (13/13) versus 60% (6/10), and 90% (9/10) versus 78% (7/9), respectively.

A satisfactory bacteriological response (cure or presumed cure) was obtained in 88% (113/129) and 78% (97/125) of bacteriologically evaluable patients treated with grepafloxacin or clarithromycin, respectively ($p = 0.04$, 95% CI = 0.00, 0.20). Seven patients in the grepafloxacin group and 11 patients in the clarithromycin group were failures or presumed failures. Seven and 10 patients, respectively, in the grepafloxacin and clarithromycin groups were classified as cures

Table V. Antimicrobial susceptibility of pretreatment isolates of primary pathogens

Pathogen	Antimicrobial agent	No.	Susceptibility frequencies [no. (%)]		
			susceptible	intermediate	resistant
<i>Haemophilus influenzae</i>	Grepafloxacin	96	96 (100)		
	Clarithromycin	96	81 (84)	8 (8)	7 (7)
<i>Streptococcus pneumoniae</i>	Grepafloxacin	28	28 (100)		
	Clarithromycin	28	23 (82)		5 (18)
	Penicillin	28	20 (71)	5 (18)	3 (11)
<i>Moraxella catarrhalis</i>	Grepafloxacin	32	32 (100)		
	Clarithromycin	32	32 (100)		
<i>H. parainfluenzae</i>	Grepafloxacin	173	173 (100)		
	Clarithromycin	173	129 (75)	30 (17)	14 (8)
<i>Staphylococcus aureus</i>	Grepafloxacin	25	24 (96)		1 (4)
	Clarithromycin	25	21 (84)		4 (16)

Table VI. Summary of the most common^a drug-related adverse events reported by patients with acute bacterial exacerbations of chronic bronchitis treated with grepafloxacin or clarithromycin

Adverse event ^b	Grepafloxacin (10 days) [n = 192; no. (%)]	Clarithromycin (10 days) [n = 187; no. (%)]	p-Value ^c
Gastrointestinal (GI) system			
Total patients with one or more GI events	24 (13)	30 (16)	0.38
Diarrhoea/loose bowel movements	7 (4)	9 (5)	0.62
Nausea	10 (5)	8 (4)	0.81
Disturbance of sense of taste	11 (6)	12 (6)	0.83
Abnormal/unusual taste	9 (5)	19 (10)	0.05
Total patients with one or more drug-related adverse events	48 (25)	62 (33)	0.09

a Occurring with an incidence of 5% or greater.

b Adverse events are not necessarily additive since some patients reported more than one adverse event.

c Treatment comparisons of incidence were performed using Fisher's exact test. Values less than 0.05 were significant.

with superinfection, while one and seven patients, respectively, were failures with superinfection. One patient in the grepafloxacin group had a recurrence.

Tolerability Evaluations

There were no statistically significant differences in drug-related adverse events between patients in the two treatment groups (table VI). The most common drug-related adverse events were nausea, diarrhoea, taste disturbance and abnormal taste.

Six patients (3%) in each treatment group withdrew from the study because of adverse events. In seven of these patients, the events were judged by the investigator to be drug related, including four patients in the grepafloxacin treatment group (drug-related adverse events included diarrhoea, dizziness, drowsiness, nausea, vomiting and skin rash) and three patients in the clarithromycin treatment group (drug-related adverse events included abnormal taste, nausea, feeding problems, gastrointestinal distress, skin rash and tinnitus). Five serious adverse events were reported, none of which were considered drug related.

Discussion

The results of this study indicated that once-daily administration with grepafloxacin 400mg for 10 days is as well tolerated and clinically effective as twice-daily administration with clarithromycin 500mg for 10 days in the treatment of patients with ABECB.

The clinical cure or improvement rates reported at follow-up in this study (88 and 89% in the grepafloxacin and clarithromycin groups, respectively) were similar to those observed in previous clinical comparisons of 10-day treatments for ABECB with grepafloxacin and amoxicillin (82 vs 85%)^[21] and grepafloxacin and ciprofloxacin (87 vs 80%).^[22] Collectively, these studies confirm the clinical efficacy of grepafloxacin in the treatment of ABECB.

Patients in the grepafloxacin group demonstrated marked improvement within 4 to 6 days

after initiation of therapy (the first during-treatment measurement) as indicated by substantial decreases in the incidence and severity of symptoms. Improvement continued and was maintained throughout the study. Improvements were comparable in the clarithromycin treatment group.

While the clinical efficacies of grepafloxacin and clarithromycin were equivalent in the present study, the bacteriological cure rates of the two treatments approached but did not meet the criteria for equivalence. When bacteriological success was assessed as a function of infecting organism in the present study, patients in the grepafloxacin treatment group showed microbiological cure rates comparable to those seen in the clarithromycin group for patients yielding *S. pneumoniae* or *H. parainfluenzae*.

Treatment with grepafloxacin 400mg once daily for 10 days was associated with a low incidence of drug-related adverse events similar to that seen with clarithromycin. The most common drug-related adverse events reported in both treatment groups were nausea, diarrhoea, taste disturbance and abnormal taste. The majority of these were mild to moderate in severity and few patients withdrew from the study as a result of drug-related adverse events.

The choice of an oral antibiotic for the treatment of ABECB requires not only consideration of clinical and bacteriological efficacy and tolerability profile, but also consideration of dosage convenience. Patient compliance with oral antibiotic therapy is known to correlate with the dosage regimen. Mean compliance rates of 80, 60 and 38% were found when oral antibiotics were administered once, twice and three times a day, respectively.^[23] Therefore, grepafloxacin 400mg once daily may have positive effects on patient adherence to therapy compared with antibiotics that require more frequent dose administration.

Conclusions

In conclusion, grepafloxacin 400mg once daily for 10 days was as well tolerated and clinically effective as a 10-day course of clarithromycin 500mg

twice daily for patients with ABECB. Grepafloxacin was associated with a marked reduction in the proportion of patients with symptoms of ABECB and substantial improvement in the severity of symptoms within 4 to 6 days (the first during-treatment measurement) of beginning treatment.

The broad-spectrum antibacterial activity of grepafloxacin, including excellent activity against the major bacterial pathogens of the lower respiratory tract (Gram-positive, Gram-negative and atypical organisms), continued activity against multidrug-resistant isolates, as well as excellent penetration into lung tissues, supports its use in the treatment of this lower respiratory tract infection.

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