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Double-Blind, Randomized Study of the Efficacy and Safety of Oral Pharmacokinetically Enhanced Amoxicillin-Clavulanate (2,000/125 Milligrams) versus Those of Amoxicillin-Clavulanate (875/125 Milligrams), Both Given Twice Daily for 7 Days, in Treatment of Bacterial Community-Acquired Pneumonia in Adults

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This randomized, double-blind, noninferiority trial was designed to demonstrate that pharmacokinetically enhanced amoxicillin-clavulanate (2,000/125 mg) was at least as effective clinically as amoxicillin-clavulanate 875/125 mg, both given twice daily for 7 days, in the treatment of community-acquired pneumonia in adults. In total, 633 clinically and radiologically confirmed community-acquired pneumonia patients (intent-to-treat population) were randomized to receive either oral amoxicillin-clavulanate 2,000/125 mg ($n = 322$) or oral amoxicillin-clavulanate 875/125 mg ($n = 311$). At screening, 160 of 633 (25.3%) patients had at least one typical pathogen isolated from expectorated or invasive sputum samples or blood culture (bacteriology intent-to-treat population). *Streptococcus pneumoniae* (58 of 160, 36.3%), methicillin-susceptible *Staphylococcus aureus* (34 of 160, 21.3%), and *Haemophilus influenzae* (33 of 160, 20.6%) were the most common typical causative pathogens isolated in both groups in the bacteriology intent-to-treat population. Clinical success in the clinical per protocol population at test of cure (days 16 to 37), the primary efficacy endpoint, was 90.3% (223 of 247) for amoxicillin-clavulanate 2,000/125 mg and 87.6% (198 of 226) for amoxicillin-clavulanate 875/125 mg (treatment difference, 2.7; 95% confidence interval, −3.0, 8.3). Bacteriological success at test of cure in the bacteriology per protocol population was 86.6% (58 of 67) for amoxicillin-clavulanate 2,000/125 mg and 78.4% (40 of 51) for amoxicillin-clavulanate 875/125 mg (treatment difference, 8.1%; 95% confidence interval, −5.8, 22.1). Both therapies were well tolerated. Amoxicillin-clavulanate 2,000/125 mg twice daily was shown to be as clinically effective as amoxicillin-clavulanate 875/125 mg twice daily for 7 days in the treatment of adult patients with community-acquired pneumonia, without a noted increase in the reported rate of adverse events.

Community-acquired pneumonia is a common disease that is potentially life threatening, especially in older adults and those with other morbid risk factors (9). Although many pathogens have been associated with community-acquired pneumonia, the most significant pathogen remains *Streptococcus pneumoniae* (12). *S. pneumoniae* is not only the most common pathogen but is also associated with the greatest morbidity and mortality (12). Therefore, it is vital that any empirical antibiotic therapy for community-acquired pneumonia be effective against the pneumococcus and take into consideration the local prevalence of antibacterial resistance (1).

Recently published guidelines on the management of community-acquired pneumonia for adults recommend empirical therapy which is effective against *S. pneumoniae* (as well as atypical pathogens) (17, 19). Additionally, the guidelines recommend the need to consider the possibility of drug-resistant *S. pneumoniae* isolates. Although the relationship between poor clinical outcomes and community-acquired pneumonia caused by resistant *S. pneumoniae* has not been clearly demonstrated, limited reports have implicated *S. pneumoniae* isolates with high penicillin resistance in the increased mortality rate for patients who survived the first few days of hospitalization (7, 8).

A new, pharmacokinetically enhanced bilayer formulation of the β-lactam antibiotic amoxicillin-clavulanate (at a dose of 2,000/125 mg, or two 1,000/62.5 mg tablets twice daily), provides immediate release of clavulanate and both immediate and sustained release of amoxicillin to maintain serum concentrations of amoxicillin that exceed the MIC for the target pathogen for an extended period of the dosing interval (2, 16, 21). The pharmacokinetic and pharmacodynamic properties of this new formulation predict high rates of bacteriological success against respiratory tract infection pathogens, including *S. pneumoniae* isolates with reduced susceptibility to penicillin (penicillin-resistant *S. pneumoniae* [PRSP]) and/or amoxicillin (*S. pneumoniae* with amoxicillin MICs of ≤4 μg/ml) (2, 21).

This study was conducted to investigate the suitability of the pharmacokinetically enhanced formulation of amoxicillin-clavulanate (2,000/125 mg), a β-lactam antibiotic, in the treatment of adults patients with community-acquired pneumonia.

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MATERIALS AND METHODS

This study was carried out in 102 centers worldwide from February 2001 to March 2002 (Table 1). The study was conducted in accordance with Good

TABLE 1. Patient distribution by center worldwide

Region or country	No. of centers	No. of patients randomized
Europe	44	334
Asia	6	49
Russia	4	9
South Africa	2	13
United States	46	228
Total	102	633

Clinical Practice and the Declaration of Helsinki as amended in Somerset West, Republic of South Africa, in 1996. The protocol was approved by local ethics committees for all centers. All patients gave written, dated, informed consent before entering the study.

Study design. This randomized, double-blind, double-dummy, parallel group study utilized a noninferiority design to compare the efficacy and safety of amoxicillin-clavulanate 2,000/125 mg with amoxicillin-clavulanate 875/125 mg in treating adult community-acquired pneumonia patients. Noninferiority would be concluded if the lower limit of the 95% confidence interval of the treatment difference in the proportion of successes between the treatment groups (amoxicillin-clavulanate 2,000/125 mg group minus amoxicillin-clavulanate 875/125 mg group) was no less than −10%. Eligible patients were randomized 1:1 to receive 7 days of twice-daily treatment with either two tablets of oral amoxicillin-clavulanate 1,000/62.5 mg plus one tablet of matching placebo amoxicillin-clavulanate 875/125 mg or one amoxicillin-clavulanate 875/125 mg tablet plus two tablets of matching placebo amoxicillin-clavulanate 1,000/62.5 mg. Study medication was to be taken at the start of a meal in both the morning and the evening. Patients were treated either in the hospital or on an outpatient basis.

Eligibility criteria. Male and female patients at least 16 years of age were eligible for enrollment if they had a clinical and radiological diagnosis of community-acquired pneumonia suspected to be due to typical pathogens (based on a chest radiograph and physician assessment), a fever (oral temperature of over 38°C, tympanic temperature of over 38.5°C, or rectal temperature of over 39°C), and at least one of the following: new or increased cough; purulent sputum or a change in sputum characteristics; pulmonary rales and/or evidence of pulmonary consolidation; dyspnea or tachypnea; an elevated total peripheral white blood cell count or >15% immature neutrophils or leukopenia; or hypoxemia. Radiological diagnosis of community-acquired pneumonia was based on the presence of new or progressive infiltrate(s) or consolidation consistent with pneumonia and was made within 48 h prior to randomization. All chest X-rays performed at screening were confirmed by either a radiologist or an investigator who was a pulmonary specialist or infectious diseases physician.

Excluded from the study were patients with (i) a known or suspected hypersensitivity to penicillin or β-lactam antibacterials; (ii) pneumonia suspected to be due to atypical pathogens; (iii) hospital-acquired pneumonia; (iv) aspiration or postobstructive pneumonia; (v) cystic fibrosis, active tuberculosis, bronchiectasis, or active pulmonary malignancies; (vi) disseminated infection or complicating infection or disease that required parenteral antibacterial therapy or would have compromised evaluation of the study treatment; (vii) >24 h of oral antibacterial treatment or one injection of an intramuscular therapy of ceftriaxone within 7 days; (viii) infectious mononucleosis; (ix) known or suspected renal impairment or known creatinine clearance of <30 ml/min; (x) known or suspected hepatic impairment, a history of cholestatic jaundice, or hepatic dysfunction attributed to taking amoxicillin-clavulanate; (xi) immunodeficiency or human immunodeficiency virus infection with a CD4 count of <200 cells/mm^3; (xii) life-threatening or serious unstable underlying disease; or (xiii) alcohol or drug abuse. Also excluded from the study were patients under treatment with tubular secretion inhibitors or treatment with any other investigational drug or device within 30 days (or five half-lives) prior to study entry. Patients who did not have a *Legionella* urine antigen test or for whom such a test was positive were excluded. Women who were pregnant or breastfeeding were excluded. Not excluded from the study were patients with chronic obstructive pulmonary disease.

Clinical and radiological assessments. Clinical response at test of cure was the primary efficacy variable in the study. Patients were required to attend the clinic four times for assessment: at screening (day 0), on-therapy (days 3 to 5), end of therapy (days 9 to 11), and test of cure (days 28 to 35). For the purpose of analyses of the per protocol population, the visit windows were extended prior to unblinding to days −2 to 1 for screening, days 2 to 7 for on-therapy, days 8 to 15 for end of therapy, and days 16 to 37 for test of cure. This extension was made to ensure that all clinically relevant data were included in the analyses. As all randomized patients were included in the intent-to-treat analysis, data for the intent-to-treat population were not restricted to the specified visit windows.

Clinical assessment was made on the basis of signs and symptoms of community-acquired pneumonia. A clinical outcome of success at either end of therapy or test of cure was defined as sufficient improvement in the signs and symptoms of pneumonia recorded at screening such that no additional antibacterial therapy was indicated. For clinical outcome of success to be made at the test-of-cure visit (second posttherapy visit), patients had to be considered to have a clinical outcome of success at the end of therapy (first posttherapy visit).

Radiological outcome, a secondary efficacy variable, was assessed by comparison of the chest X-rays performed at the test of cure with those performed at screening. For patients who were clinical failures or withdrew from the study, a chest X-ray was carried out at the time of failure or withdrawal. Each patient's radiological outcome was defined as improved, unchanged, worse (a worsening of the baseline radiological signs of community-acquired pneumonia or the appearance of new radiological signs of community-acquired pneumonia), and unable to determine (a valid assessment of radiological outcome could not be made; i.e., if the patient was lost to follow-up).

Bacteriological assessment. Bacterial response to treatment was a secondary efficacy variable in the study. At screening, all patients provided a sputum or invasive respiratory sample as well as two sets of blood culture samples. Additional bacteriological specimens were collected at the subsequent visits where possible, clinically indicated, or for withdrawals. Sputum samples were evaluated by Gram stain for purulence, defined as >25 white blood cells and <10 squamous epithelial cells per field at 100× magnification. Purulent sputum, invasive respiratory, and blood samples were cultured at the local laboratories. All pathogens isolated were sent to the central laboratory for confirmation of identification and for susceptibility testing by a broth microdilution method according to National Committee for Clinical Laboratory Standards (NCCLS) guidelines (18). Amoxicillin-clavulanic acid was tested in a 2:1 ratio. MICs were expressed in terms of the amoxicillin concentration. Isolates of *Haemophilus* spp., *Moraxella catarrhalis*, *Enterococcus* spp., and *Staphylococcus aureus* were tested for β-lactamase production. Currently, there are no NCCLS breakpoints for the 2,000/125 mg formulation of amoxicillin-clavulanate.

All patients had serological testing performed for atypical pathogens on paired sera (predose and test of cure) by the central laboratory and MRL Diagnostics (Cypress, Calif.). The atypical pathogens tested in the study and their corresponding criteria for a positive result were as follows: (i) *Legionella pneumophila*, a ≥4-fold rise in antibody titer (indirect fluorescent antibody; Zeus Scientific) between screening and test of cure; (ii) *Mycoplasma pneumoniae*, immunoglobulin G (IgG) testing (enzyme-linked immunosorbent assay; Wampole Laboratories) with an immune status ratio of ≥1.1 at test of cure and rise in immune status ratio of ≥46% between screening and test of cure; or IgM testing (enzyme-linked immunosorbent assay) with an immune status ratio of ≥1.1 at screening and/or test of cure; (iii) *Chlamydia pneumoniae* and *Chlamydia psittaci*, a ≥4-fold rise in IgG titer (microimmunofluorescent antibody) between screening and test of cure; or IgG titer ≥1:16, IgM titer ≥1:10, and IgA titer ≥1:16 in a single visit. A urine sample was collected before the first dose of study medication to test for *Legionella pneumophila* serogroup 1 antigen with a *Legionella* urinary antigen enzyme immunoassay (Binax). Patients with a positive result were not randomized.

The bacteriological outcome was categorized as eradication or presumed eradication at end of therapy or test of cure if all initial pathogens were absent or if there was clinical evidence of eradication in the absence of an evaluable sample. The outcome at end of therapy (first posttherapy visit) was categorized as persistence or presumed persistence if the original pathogen was still present or the patient had a clinical response of failure. The bacteriological outcome at test of cure (second posttherapy visit) was classified as failure or presumed failure if the original pathogen was still present or had recurred or if the patient had had bacteriological response of failure at the previous visit. An outcome of unable to determine referred to the cases where an assessment could not be made (i.e., lost to follow-up). If a new pathogen was identified in a symptomatic patient at end of therapy or test of cure, the outcome was termed superinfection or new infection, respectively; however, if a new pathogen was identified in an asymptomatic patient, the outcome was defined as colonization.

Safety assessment. All patients who received at least one dose of the study drug were included in the safety analysis. All patients in the study were monitored for clinical as well as laboratory adverse events. Adverse events did not include anticipated day-to-day fluctuations of existing conditions. Adverse events were recorded on-therapy and for 30 days after therapy, and their severity and relationship to the study medication were assessed by the investigator. Any

TABLE 2. Attrition of patient populations in the study

Population[a]	No. of patients in amoxicillin-clavulanate treatment group:	
	2,000/125 mg	875/125 mg
ITT population (safety population)	322	311
Protocol violation	(56)	(69)
Clinical PP end of therapy	266	242
Protocol violation	(19)	(16)
Clinical PP test of cure	247	226
ITT population (safety population)	322	311
No typical pathogen isolated	(235)	(238)
Bacteriology ITT	87	73
Protocol violation	(13)	(16)
Bacteriology PP end of therapy	74	57
Protocol violation	(7)	(6)
Bacteriology PP test of cure	67	51

[a] The most common protocol violations for exclusion from the clinical per protocol (PP) population were no community-acquired pneumonia lack of visit compliance, indeterminate clinical assessment, lack of study medication compliance, and concomitant medication violation. The most common protocol violations for exclusion from the bacteriology per protocol population were lack of visit compliance, indeterminate bacteriological and/or clinical assessment, concomitant medication violation, lack of study medication compliance and complicating infections. ITT, intent to treat.

patient who withdrew from the study or who was a clinical failure underwent a safety evaluation at the time of leaving the study.

Statistical analysis. The primary objective was to demonstrate noninferiority of amoxicillin-clavulanate 2,000/125 mg to amoxicillin-clavulanate 875/125 mg. The primary efficacy variable was the clinical response at test of cure in the clinical per protocol population. The primary efficacy analysis was based on an unstratified comparison of proportions between treatment groups in the clinical per protocol population. Two-sided 95% confidence intervals were used to estimate the difference in the proportion of successes between the treatment groups, calculated with the normal approximation to the binomial distribution.

Fisher's exact test was used to test for a difference in the proportion of patients with the most frequently observed adverse events.

In order to achieve a power of 90%, the study was designed to enroll 634 patients in order to have ≈220 evaluable patients in each treatment arm, assuming an underlying equivalent clinical response of 88% at test of cure and that as many as 30% of patients would be ineligible for the clinical per protocol population.

Four population sets were identified for the analysis of this study. The intent-to-treat population comprised all randomized patients who took at least one dose of study medication. The clinical per protocol population was a subset of the intent-to-treat population and excluded those who violated the protocol to a degree that might affect treatment efficacy. The bacteriology intent-to-treat population was also a subset of the intent-to-treat population. Since the study medications were not expected to cover atypical pathogens, only those patients with at least one typical pathogen isolated at screening, including patients with both a typical and an atypical pathogen, were included in the bacteriology intent-to-treat population. Patients with only an atypical pathogen identified by serology were excluded from the bacteriology intent-to-treat population but included in the clinical intent-to-treat and, if there were no protocol violations, clinical per protocol populations for clinical efficacy and safety assessments. The bacteriology per protocol population was a subset of the bacteriology intent-to-treat population, excluding all those patients who violated the study protocol to an extent that might affect treatment efficacy or the assessment of efficacy.

RESULTS

A total of 634 patients were randomized, of whom 633 received study medication and were included in the intent-to-treat and safety populations. The patient populations are presented in detail in Table 2. The demographic profiles of the two groups were well matched in ethnic origin (amoxicillin-clavulanate 2,000/125 mg versus 875/125 mg: white, 278 of 322 [86.3%] versus 268 of 311 [86.2%]; black, 10 of 322 [3.1%] versus 13 of 311 [4.2%]; other, 34 of 322 [10.6%] versus 30 of 311 [9.6%]); age (amoxicillin-clavulanate 2,000/125 mg versus 875/125 mg: mean [standard deviation] age, 50.8 [19.3] versus 48.7 [18.8] years); smoking history (amoxicillin-clavulanate 2,000/125 mg versus 875/125 mg: current smoker, 108 of 322 [33.5%] versus 111 of 311 [35.7%]; ever smoked, 185 of 322 [57.5%] versus 164 of 311 [52.7%]; smoking pack-years >0 to 30, 145 of 322 [45.0%] versus 120 of 311 [38.6%]; and smoking pack-years >30, 38 of 322 [11.8%] versus 39 of 311 [12.5%]).

There was a slightly larger proportion of males in the amoxicillin-clavulanate 2,000/125 mg group (188 of 322 [58.4%]) than in the comparator group (164 of 311 [52.7%]). The baseline clinical characteristics of the two groups were also similar (Table 3). A modified Fine mortality risk class was assessed in the study in which missing data points were assigned a value of zero. In addition, oxygen saturation measured by pulse oximetry was substituted for analysis of arterial blood gases, and arterial blood pH was not measured. In the intent-to-treat population, the overall distribution of patients by mortality risk class was: in the amoxicillin-clavulanate 2,000/125 mg group, class I to III (92.5%), class IV (6.5%), and class V (0.9%), and in the amoxicillin-clavulanate 875/125 mg group, class I to III (93.6%), class IV (5.1%), and class V (1.3%). At entry, 75 of 322 (23.3%) patients in the amoxicillin-clavulanate 2,000/125 mg group and 6 of 311 (22.2%) in the comparator group were hospitalized. For patients who were treated in hospital, the majority had a low mortality risk class of ≤III (Table 3).

Overall rates of patients completing the study were high in both groups (amoxicillin-clavulanate 2,000/125 mg, 289 of 322 [89.8%]; amoxicillin-clavulanate 875/125 mg, 265 of 311 [85.2%]). The most common reason for withdrawal from the study in both groups was lost to follow-up (12 of 322 [3.7%], amoxicillin-clavulanate 2,000/125 mg; 16 of 311 [5.1%], amoxicillin-clavulanate 875/125 mg). Other reasons for withdrawal were protocol deviations, adverse events, insufficient therapeutic effect, and withdrawal of consent.

The majority of patients in both treatment groups followed the protocol while in the study and were included in the per protocol populations. The most common protocol violations were medication compliance, no community-acquired pneumonia diagnosed, outcome of unable to determine, prohibited concomitant medications, and complicating infections (Table 2).

Bacteriology at screening. A total of 87 of 322 patients (27.0%) in the amoxicillin-clavulanate 2,000/125 mg group and 73 of 311 (23.5%) in the amoxicillin-clavulanate 875/125 mg group had at least one typical pathogen identified at screening. The most commonly identified typical pathogen was *S. pneumoniae* in both treatment groups (Table 4). A total of 61 patients (61 of 322 [18.9%]) in the amoxicillin-clavulanate 2,000/125 mg group and 82 in the comparator group (82 of 311 [26.4%]) had serology results indicative of atypical pathogens without having a typical pathogen identified at screening. This group of patients was not included in the bacteriology intent-to-treat population.

At screening, of the seven patients (7 of 322 [2.2%]) in the amoxicillin-clavulanate 2,000/125 mg group who had a pathogen isolated from blood culture, three had *S. pneumoniae* isolates, including one isolate that was of intermediate suscepti-

TABLE 3. Baseline clinical characteristics[a]

Clinical characteristic	No. (%) of patients			
	ITT population		Clinical PP population	
	2,000/125 mg (n = 322)	875/125 mg (n = 311)	2,000/125 mg (n = 247)	875/125 mg (n = 226)
Fever or history of fever	321 (99.7)	310 (99.7)	247 (100)	226 (100)
Altered total white blood cell count	134 (41.6)	127 (40.8)	91 (36.8)	89 (39.4)
Sputum				
Purulent	290 (90.1)	278 (89.4)	221 (89.5)	203 (89.8)
Change in characteristics	217 (67.4)	201 (64.6)	159 (64.4)	146 (64.6)
New or increased cough	319 (99.1)	311 (100)	244 (98.8)	226 (100)
Signs of pneumonia				
Cough	319 (99.1)	311 (100)	244 (98.8)	226 (100)
Dyspnea	233 (72.4)	233 (74.9)	173 (70.0)	168 (74.3)
Tachypnea	190 (59.0)	186 (59.8)	142 (57.5)	133 (58.8)
Hypoxemia	48 (14.9)	43 (13.8)	36 (14.6)	31 (13.7)
Pleuritic chest pain	215 (66.8)	234 (75.2)	160 (64.8)	169 (74.8)
Auscultatory finding				
Rales	271 (84.2)	265 (85.2)	205 (83.0)	191 (84.5)
Pulmonary consolidation	181 (56.2)	169 (54.3)	131 (53.0)	116 (51.3)
Chest X-ray consistent with pneumonia	308 (95.7)	296 (95.2)	247 (100)	226 (100)
Preexisting COPD at screening	54 (16.8)	49 (15.8)	36 (14.6)	40 (17.7)
In-patient at screening	75 (23.3)	69 (22.2)	58 (23.5)	47 (20.8)
Mortality risk class for inpatients				
Low				
Class I (% of inpatients)	23 (30.7)	21 (30.4)	21 (36.2)	17 (36.2)
Class II (% of inpatients)	15 (20.0)	19 (27.5)	10 (17.2)	10 (21.3)
Class III (% of inpatients)	20 (26.7)	15 (21.7)	18 (31.0)	11 (23.4)
Moderate				
Class IV (% of inpatients)	15 (20.0)	10 (14.5)	8 (13.8)	8 (17.0)
High				
Class V (% of inpatients)	2 (2.7)	4 (5.8)	1 (1.7)	1 (2.1)

[a] ITT, intent to treat; PP, per protocol; COPD, chronic obstructive pulmonary disease.

bility to penicillin (penicillin MIC = 1 μg/ml). Of the five patients (5 of 311 [1.6%]) in the comparator group who were bacteremic, two had *S. pneumoniae* isolates, both susceptible to penicillin. The remaining pathogens isolated from bacteremic patients were methicillin-susceptible *Staphylococcus aureus* (MSSA) (one in each treatment group), *Klebsiella oxytoca*, *Moraxella catarrhalis*, and *Streptococcus* spp. (one of each in the amoxicillin-clavulanate 2,000/125 mg group), and *Acinetobacter lwoffi* and *Klebsiella pneumoniae* (one of each in the amoxicillin-clavulanate 875/125 mg group).

A total of 6 of 33 (18.2%) of *S. pneumoniae* isolates from the amoxicillin-clavulanate 2,000/125 mg group and 3 of 28 (10.7%) from the amoxicillin-clavulanate 875/125 mg group were nonsusceptible (intermediate and resistant) to penicillin (penicillin MIC, ≥0.12 μg/ml), according to NCCLS guidelines (18). The overall range of penicillin MICs for *S. pneumoniae* was ≤0.015 to 4 μg/ml. None of the *S. pneumoniae* isolates in the amoxicillin-clavulanate 2,000/125 mg group and 2 of 28 (7.1%) in the amoxicillin-clavulanate 875/125 mg group had an amoxicillin-clavulanic acid MIC of ≥4/2 μg/ml, the current

TABLE 4. Common pathogens identified at screening in patients with at least one typical or atypical pathogen[a]

Patient group	No. (%) of patients in amoxicillin-clavulanate treatment group:	
	2,000/125 mg	875/125 mg
Patients with at least one typical or atypical pathogen	148	155
Patients with at least one typical pathogen isolated from cultures	87	73
S. pneumoniae	31 (35.6)	27 (37.0)
H. influenzae	20 (23.0)	13 (17.8)
Methicillin-susceptible *Staphylococcus aureus*	16 (18.4)	18 (24.7)
M. catarrhalis	4 (4.6)	3 (4.1)
Seropositive for atypical pathogens	29 (33.3)	21 (28.8)
Patients with at least one atypical pathogen by serologic testing	90	103
M. pneumoniae	69 (76.7)	85 (82.5)
C. pneumoniae	23 (25.6)	22 (21.4)
L. pneumophila	2 (2.2)	1 (1.0)
C. psittaci	3 (3.3)	1 (1.0)

[a] Typical pathogens were isolated from sputum or respiratory sample or blood culture. Atypical pathogens were identified by serologic testing.

TABLE 5. Overall clinical, radiological, and bacteriological efficacy results at test of cure or end of therapy

Population[a]	Success rate, no. of successes/no. in group (% successes), amoxicillin-clavulanate 2,000/125 mg vs amoxicillin-clavulanate 875/125 mg	Treatment difference, % (95% CI)
Clinical response at test of cure		
Clinical PP population[b]	223/247 (90.3) vs 198/226 (87.6)	2.7 (−3.0, 8.3)
ITT population	274/322 (85.1) vs 243/311 (78.1)	7.0 (0.9, 13.0)
Clinical response at end of therapy		
Clinical PP population	250/266 (94.0) vs 223/242 (92.1)	1.8 (−2.6, 6.3)
ITT population	291/322 (90.4) vs 264/311 (84.9)	5.5 (0.4, 10.6)
Bacteriological response at test of cure		
Bacteriology PP population	58/67 (86.6) vs 40/51 (78.4)	8.1 (−5.8, 22.1)
Bacteriology ITT population	73/87 (83.9) vs 49/73 (67.1)	16.8 (3.5, 30.0)
Bacteriological response at end of therapy		
Bacteriology PP population	67/74 (90.5) vs 47/57 (82.5)	8.1 (−3.8, 20.0)
Bacteriology ITT population	75/87 (86.2) vs 57/73 (78.1)	8.1 (−3.8, 20.1)
Radiological response at test of cure		
Clinical PP population	230/247 (93.1) vs 204/226 (90.3)	2.9 (−2.1, 7.8)
ITT population	281/322 (87.3) vs 254/311 (81.7)	5.6 (−0.0, 11.2)

[a] See Table 3, footnote *a*.
[b] Primary efficacy endpoint.

breakpoint for nonsusceptible *S. pneumoniae* to the conventional formulation of amoxicillin-clavulanic acid (18) (overall amoxicillin MIC range, ≤0.015 to 8 μg/ml). Four of the 33 (12.1%) *Haemophilus influenzae* isolates tested (three in the amoxicillin-clavulanate 2,000/125 mg group and one in the amoxicillin-clavulanate 875/125 mg group) produced β-lactamase.

Clinical responses. The clinical success rate in the clinical per protocol population at test of cure (days 16 to 37, second posttherapy visit, primary efficacy endpoint) was 90.3% (223 of 247) for amoxicillin-clavulanate 2,000/125 mg and 87.6% (198 of 226) for amoxicillin-clavulanate 875/125 mg (treatment difference, 2.7; 95% confidence interval, −3.0, 8.3). The primary and all secondary efficacy parameters are detailed in Table 5. In the intent-to-treat population at test of cure and end of therapy, the clinical success rates were slightly lower because patients with an unable to determine clinical outcome were classified as failures at that visit.

The clinical success rate at test of cure in the clinical per protocol population was comparable in the two treatment groups for patients with low mortality risk (risk classes I to III): 90.6% (213 of 235), amoxicillin-clavulanate 2,000/125 mg; 89.2% (189 of 212), amoxicillin-clavulanate 875/125 mg group. The clinical success rate at the test of cure visit in the same population for moderate mortality risk class of IV was 90.9% (10 of 11) in the amoxicillin-clavulanate 2,000/125 mg group and 69.2% (9 of 13) in the amoxicillin-clavulanate 875/125 mg group, though the number of patients in this category was low. Only two patients with a high mortality risk class of V, one in each treatment group, were in the clinical per protocol population at test of cure. Both patients were clinical failures.

In the intent-to-treat population, the clinical success rate at test of cure for bacteremic patients was similar for both therapies. In the amoxicillin-clavulanate 2,000/125 mg group, five of seven bacteremic patients (71.4%) were clinical successes, and in the comparator group, four of five (80.0%) were clinical successes. The two failures in the amoxicillin-clavulanate 2,000/125 mg group were one patient with β-lactamase-negative *M. catarrhalis* and one patient with β-lactamase positive MSSA. The patient with β-lactamase positive MSSA was classified as unable to determine because the patient was lost to follow-up. The single failure in the amoxicillin-clavulanate 875/125 mg group was a patient with *Klebsiella pneumoniae* who was also lost to follow-up.

In the bacteriology per protocol population at test of cure, clinical success rates for patients with typical pathogens were comparable in both treatment groups. In patients with *S. pneumoniae*, the clinical success rate was 96.3% (26 of 27) for amoxicillin-clavulanate 2,000/125 mg and 84.2% (16 of 19) for amoxicillin-clavulanate 875/125 mg, respectively. In patients with MSSA, the clinical success rate was 100% (11 of 11) for amoxicillin-clavulanate 2,000/125 mg and 84.6% (11 of 13) for amoxicillin-clavulanate 875/125 mg. The clinical success rate in patients with *H. influenzae* was slightly lower in the amoxicillin-clavulanate 2,000/125 mg group, 87.5% (14 of 16), compared to 100% (10 of 10) in the same population in the amoxicillin-clavulanate 875/125 mg group (Table 6). At the test-of-cure visit in the clinical per protocol population, clinical success rates for patients with typical pathogens only, both typical and atypical pathogens, and atypical pathogens only were 86.0% (37 of 43), 96.3% (26 of 27), and 91.5% (43 of 47), respectively for amoxicillin-clavulanate 2,000/125 mg and 88.6% (31 of 35), 70.6% (12 of 17) and 88.9% (56 of 63) for amoxicillin-clavulanate 875/125 mg (Table 7), respectively.

Bacteriologic responses. Bacteriological success rates (eradication or presumed eradication) at test of cure and end of therapy are provided in Table 5.

The bacteriological success rates at test of cure against *S. pneumoniae* isolates in the bacteriology per protocol population were 96.2% (25 of 26) for amoxicillin-clavulanate 2,000/125 mg and 77.8% (14 of 18) for amoxicillin-clavulanate 875/125 mg. In addition to the patients included in the bacteriology per protocol population analysis, a further 14 in the bacteriology intent-to-treat population had *S. pneumoniae* isolated at screening. Of these, five of five (100%) treated with amoxicillin-clavulanate 2,000/125 mg and two of nine (22.2%) treated

TABLE 6. Clinical success rate at test of cure for typical pretherapy pathogens[a]

Patient group or pathogen	No. of successes/no. in group (% successes)			
	Bacteriology ITT population		Bacteriology PP population	
	2,000/125 mg	875/125 mg	2,000/125 mg	875/125 mg
Patients with at least one typical pathogen	87	73	67	51
S. pneumoniae[b]	32/33 (97.0)	19/28 (67.9)	26/27 (96.3)	16/19 (84.2)
H. influenzae	17/20 (85.0)	12/13 (92.3)	14/16 (87.5)	10/10 (100)
Methicillin-susceptible *Staphylococcus aureus*	15/16 (93.8)	12/18 (66.7)	11/11 (100)	11/13 (84.6)
M. catarrhalis	3/4 (75.0)	3/3 (100)	1/2 (50.0)	2/2 (100)

[a] See Table 3, footnote *a*.
[b] There were 33 *S. pneumoniae* isolates from 31 patients with this pathogen in the amoxicillin-clavulanate 2,000/125 mg group; there were 28 *S. pneumoniae* isolates from 27 patients with the pathogen in the amoxicillin-clavulanate 875/125 mg group.

with amoxicillin-clavulanate 875/125 mg were successes at test of cure. Against *H. influenzae* at test of cure in the bacteriology per protocol population, the bacteriological success rate was 75.0% (12 of 16) for amoxicillin-clavulanate 2,000/125 mg and 100% (10 of 10) for amoxicillin-clavulanate 875/125 mg.

A total of four PRSP isolates were identified in the study, two in each treatment group. The two PRSP isolates in the amoxicillin-clavulanate 2,000/125 mg group both had penicillin MICs of 2 μg/ml and amoxicillin-clavulanic acid MICs of 2/1 μg/ml. One patient with PRSP in the amoxicillin-clavulanate 875/125 mg group (penicillin MIC = 2 μg/ml and amoxicillin-clavulanic acid MIC = 4/2 μg/ml) had an outcome of unable to determine and was not included in the per protocol population analysis. The remaining PRSP in the amoxicillin-clavulanate 875/125 mg group had a penicillin MIC of 4 μg/ml and an amoxicillin-clavulanic acid MIC of 8/4 μg/ml. All three PRSP isolates in the per protocol population were resistant to multiple drugs. One of the two PRSP isolates in the amoxicillin-clavulanate 2,000/125 mg group was resistant to oral cephalosporins and penicillin and the other was resistant to oral cephalosporins, macrolides, and sulfonamides. The one PRSP isolate in the amoxicillin-clavulanate 875/125 mg group was resistant to amoxicillin-clavulanic acid, oral cephalosporins, macrolides, and sulfonamides. All three patients were both clinical and bacteriological successes at test of cure.

In the bacteriology per protocol population at test of cure, β-lactamase-producing isolates identified in the amoxicillin-clavulanate 2,000/125 mg group were: 2 of 16 (12.5%) *H. influenzae*, 8 of 11 (72.7%) MSSA, and 1 of 2 (50.0%) *M. catarrhalis*. Of these patients, 10 of 11 (90.9%) were clinical and bacteriological successes. The one failure was a patient with *H. influenzae* identified at screening who had clinical evidence of persistence at end of therapy. In the amoxicillin-clavulanate 875/125 mg group, there were 15 β-lactamase-producing isolates: 1 of 10 (10.0%) *H. influenzae*, 12 of 13 (92.3%) MSSA, and 2 of 2 (100%) *M. catarrhalis*. In this group, 13 of 15 (86.7%) were clinical successes at test of cure, while 11 of 15 (73.3%) were bacteriological successes at the same time point. Two patients with MSSA in this group (one with MSSA plus *Haemophilus parainfluenzae* plus *Enterobacter aerogenes*, and the other with MSSA plus *H. parainfluenzae* plus *Pseudomonas aeruginosa*) were clinical and bacteriological failures at test of cure, and an additional two patients (one with MSSA plus *Klebsiella oxytoca* and one with MSSA plus *H. influenzae*) were clinical successes but bacteriological failures.

Safety. During the interval on-therapy and within 30 days posttherapy, 130 of 322 (40.4%) of patients in the amoxicillin-clavulanate 2,000/125 mg group and 131 of 311 (42.1%) in the amoxicillin-clavulanate 875/125 mg group reported at least one adverse event. Adverse events considered by the investigator to

TABLE 7. Clinical success rate at test of cure in patients with and without serologic evidence of atypical pathogens at screening[a]

Group	No. of successes/no. in group (% successes) in amoxicillin-clavulanate treatment group:	
	2,000/125 mg	875/125 mg
Clinical PP test of cure population	247	226
Group A (at least one typical pathogen) (groups B and C combined)	63/70 (90.0)	43/52 (82.7)
Group B (typical pathogen only)	37/43 (86.0)	31/35 (88.6)
Group C (typical and atypical pathogens)	26/27 (96.3)	12/17 (70.6)
Group D (atypical pathogen only)	43/47 (91.5)	56/63 (88.9)
Group E (at least one atypical pathogen) (groups C and D combined)	69/74 (93.2)	68/80 (85.0)
ITT population	322	311
Group A (at least one typical pathogen) (groups B and C combined)	78/87 (89.7)	53/73 (72.6)
Group B (typical pathogen only)	50/58 (86.2)	39/52 (75.0)
Group C (typical and atypical pathogens)	28/29 (96.6)	14/21 (66.7)
Group D (atypical pathogen only)	54/61 (88.5)	71/82 (86.6)
Group E (at least one atypical pathogen) (groups C and D combined)	82/90 (91.1)	85/103 (82.5)

[a] See Table 3, footnote *a*.

TABLE 8. Adverse events with a suspected or probable relationship to study medication reported by ≥1% of patients

Population or adverse event[a]	No. (%) of patients in amoxicillin-clavulanate group:	
	2,000/125 mg (n = 322)	875/125 mg (n = 311)
Patients with at ≥1 adverse event	61 (18.9)	57 (18.3)
Diarrhea	36 (11.2)	29 (9.3)
Nausea	8 (2.5)	8 (2.6)
SGPT (ALT) increased	7 (2.2)	1 (0.3)
SGOT (AST) increased	5 (1.6)	1 (0.3)
Vomiting	5 (1.6)	3 (1.0)
Genital moniliasis	4 (1.2)	2 (0.6)
Abdominal pain	2 (0.6)	7 (2.3)

[a] SGPT, serum glutamic pyruvic transaminase; ALT, alanine aminotransferase; SGOT, serum glutamic oxaloacetic transaminase; AST, aspartate aminotransferase.

be of suspected or probable relationship to study medication were reported in 61 of 322 (18.9%) patients receiving amoxicillin-clavulanate 2,000/125 mg and 57 of 311 (18.3%) patients receiving amoxicillin-clavulanate 875/125 mg (Table 8). The incidence of serious adverse events was low in both groups, 5.0% (16 of 322) in the amoxicillin-clavulanate 2,000/125 mg group and 6.4% (20 of 311) in the amoxicillin-clavulanate 875/125 mg group. Only two serious adverse events were suspected by the investigator to be related to study medication, diarrhea and allergic reaction from the amoxicillin-clavulanate 875/125 mg group. In both cases, the patients were hospitalized for the condition. Withdrawals from the study due to adverse events were also low for both groups, 2.2% (7 of 322) in the amoxicillin-clavulanate 2,000/125 mg group and 3.9% (12 of 311) in the amoxicillin-clavulanate 875/125 mg group, with pneumonia being the most frequent adverse event leading to withdrawal.

There was no statistically significant difference between the treatment groups in the incidence of the most frequently reported adverse event, diarrhea (amoxicillin-clavulanate 2,000/125 mg, 11.5% [37 of 322]; amoxicillin-clavulanate 875/125 mg, 11.9% [37 of 311]; $P = 0.90$). The majority of the diarrhea cases were mild to moderate in intensity, and there were no cases of *Clostridium difficile* colitis. Diarrhea was the cause of withdrawal for only one patient (0.3%) in each treatment group.

A total of five deaths were reported during the study, two in the amoxicillin-clavulanate 2,000/125 mg group and three in the amoxicillin-clavulanate 875/125 mg group. The reported causes of death for the patients receiving amoxicillin-clavulanate 2,000/125 mg were cardiac failure and respiratory insufficiency and cardiac arrest. In the amoxicillin-clavulanate 875/125 mg group, the reported causes of death were pulmonary carcinoma (diagnosed after the cessation of treatment with study medication), cardiac failure, and ventricular fibrillation. None were considered to be related to study medication.

One patient in the amoxicillin-clavulanate 875/125 mg group became pregnant during the study. Ultrasound confirmed the date of conception to be the day following the last dose of study medication. The pregnancy resulted in the birth of a healthy male infant 272 days after the last dose of study medication.

DISCUSSION

In this randomized, double-blind study, the primary endpoint was achieved. Amoxicillin-clavulanate 2,000/125 mg was demonstrated to be at least as effective clinically as amoxicillin-clavulanate 875/125 mg when given twice daily for 7 days in the treatment of community-acquired pneumonia in adults. Additionally, all the secondary efficacy endpoints supported the primary findings.

The result of this study is in line with similar studies with amoxicillin-clavulanate 2,000/125 mg in treating community-acquired pneumonia, in which clinical success rates for amoxicillin-clavulanate 2,000/125 mg have been shown to be in the range of 91.5 to 94.7% (13, 20) and bacteriological success rates for amoxicillin-clavulanate 2,000/125 mg have been 85.0 to 90.6% (13, 20). A recent meta-analysis of nine clinical studies (5,531 intent-to-treat patients) evaluated the bacteriological efficacy of amoxicillin-clavulanate 2,000/125 mg in the treatment of respiratory tract infections due to *S. pneumoniae*. This analysis concluded that for amoxicillin-clavulanate 2,000/125 mg, the overall bacteriological success rate in *S. pneumoniae* infections was 93.7% (60 of 67) in the comparative studies and 95.9% (348 of 363) in the noncomparative studies (10). In a similar meta-analysis of the same nine clinical studies and one additional open community-acquired pneumonia study (efficacy intent-to-treat = 6,400), the combined clinical and bacteriological success was achieved in 50 of 52 patients with PRSP, including 6 of 7 with an amoxicillin MIC of 4 μg/ml and 7 of 8 with an amoxicillin MIC of 8 μg/ml. Success rates were similar for amoxicillin-clavulanate 2,000/125 mg against PRSP for community-acquired pneumonia (96.0% [24 of 25]), acute exacerbation of chronic bronchitis (100%, [3 of 3]), and acute bacterial sinusitis (95.8%, [23 of 24]) (14).

The goal of antimicrobial therapy in treating community-acquired pneumonia with suspected or confirmed bacterial infection is to eradicate the causative pathogen, including resistant strains (1). Bacterial eradication has been shown to be correlated to improved clinical outcomes and decreased recurrence of infection. It also contributes to the prevention of the emergence and dissemination of resistant pathogens (1, 4 to 6).

The ability of antimicrobial agents to eradicate pathogens is often predicted by their pharmacodynamic and pharmacokinetic properties. For β-lactams, bactericidal effect is correlated with the time for which non-protein-bound concentrations exceed the MIC ($T > \text{MIC}$). For amoxicillin-clavulanate, a time above MIC ($T > \text{MIC}$) of 35 to 40% of the dosing interval is predictive of high bacteriological efficacy (3, 22). The new formulation of amoxicillin-clavulanate (2,000/125 mg) with sustained- and immediate-release amoxicillin provides an average $T > \text{MIC}$ of 49.4% (95% confidence interval, 47, 52) of the 12-h dosing interval for pathogens with an amoxicillin MIC of 4 μg/ml and 35% for strains with an amoxicillin MIC of 8 μg/ml (16; C. M. Kaye, GlaxoSmithKline, Welwyn, United Kingdom, data on file). The $T > \text{MIC}$ for the 875/125 mg formulation of amoxicillin-clavulanate is <35% of the dosing interval for pathogens with an amoxicillin MIC of 4 μg/ml. It would therefore be expected that amoxicillin-clavulanate 2,000/125 mg would achieve greater bacteriological success in patients with *S. pneumoniae* with elevated amoxicillin MICs and be as efficacious as amoxicillin-clavulanate 875/125 mg in eradicating

susceptible *S. pneumoniae* and β-lactamase-producing pathogens.

A total of 25.3% (160 of 633) patients had at least a typical community-acquired pneumonia pathogen isolated before entering the study, with *S. pneumoniae* (36.3%, 58 of 160) being the most predominant pathogen isolated. As has been commonly found in randomized, clinical trials of this kind, the incidence of resistant *S. pneumoniae* isolates in this study was low, two PRSP isolates in each treatment arm, with only one resistant to amoxicillin (in the amoxicillin-clavulanate 875/125 mg group). All three PRSP patients in the per protocol population were clinical successes. Several possibilities for the discrepancy of the *S. pneumoniae* resistance prevalence between this study and those reported in the Alexander Project (15) in the United States (PRSP, 25.0%) and western Europe (PRSP: France, 40.5%, and Spain, 26.4%) include that the exclusion criteria excluded patients with more severe pneumonia which could have been caused by nonsusceptible *S. pneumoniae* or serious underlying comorbidity and the local resistance prevalence at some of the countries and investigator sites within a country was low. Some countries with known high resistance prevalence (such as Spain and France) could not participate in the study.

The eradication rate of *H. influenzae* isolates in the amoxicillin-clavulanate 2,000/125 mg group was slightly lower than in the amoxicillin-clavulanate 875/125 mg group. However, because the number of patients with *H. influenzae* was low in both groups, no conclusion could be drawn about the efficacy of amoxicillin-clavulanate 2,000/125 mg against this pathogen.

Interestingly, 30.5% (193 of 633) of enrolled patients were seropositive for an atypical pathogen, although the entry criteria attempted to exclude patients with atypical pathogens. A total of 143 patients in the intent-to-treat population met the eligibility criteria (i.e., clinical symptoms at screening representative of community-acquired pneumonia caused by typical pathogens) yet were only seropositive for atypical pathogens. It is possible that these patients were infected by typical pathogens which could not be cultured (i.e., the sputum Gram stain requirements of >25 white blood cells and <10 squamous epithelial cells per field at 100× magnification were not met for sputum samples), as yields on sputum cultures in community-acquired pneumonia patients are low (11, 19).

As expected, in patients who only had typical pathogens, the clinical success rate was high in the amoxicillin-clavulanate 2,000/125 mg group (86.0% in the clinical per protocol population at test of cure). In patients who had typical pathogens and were also seropositive for atypical pathogens, the clinical success rate for amoxicillin-clavulanate 2,000/125 mg was surprisingly high (96.3% in the clinical per protocol population at test of cure). These cases may represent mixed infection or sequential infections (i.e., initial or recent infection with an atypical pathogen followed by infection with a typical pathogen, such as *S. pneumoniae*). The overall clinical response in these cases is most likely attributed to the effect of the antimicrobial on the typical pathogen. The high success rates observed indicate that the prior or concomitant presence of an atypical pathogen may not impair the efficacy of amoxicillin-clavulanate 2,000/125 mg. Furthermore, in patients who had only serologic evidence of atypical infection, both amoxicillin-clavulanate formulations achieved clinical success rates of >85%. The reasons for this apparent clinical response may be severalfold. Although a β-lactam would not be expected to be effective against atypical pathogens, serology results from these patients may have reflected recent rather than active infection caused by the atypical pathogen in question. In addition, many *Mycoplasma* and *Chlamydia* infections are mild, and clinical improvement at the test-of-cure endpoint may reflect the nature of many of these infections. Finally, there is also the possibility that the manifestations of many of these infections were due to bacterial copathogens which were not possible to isolate.

Both amoxicillin-clavulanate formulations were well tolerated. Amoxicillin-clavulanate 2,000/125 mg had a similar safety profile to that of amoxicillin-clavulanate 875/125 mg, despite the increase in the total daily dose of amoxicillin. The most commonly reported adverse event in both groups was diarrhea, in most cases mild to moderate in intensity. There was no difference in the incidence of diarrhea between the two treatment groups.

In summary, oral pharmacokinetically enhanced amoxicillin-clavulanate 2,000/125 mg was at least as effective as oral amoxicillin-clavulanate 875/125 mg when given twice daily for 7 days for the treatment of adult patients with community-acquired pneumonia. The results of this study, particularly when viewed alongside other clinical studies of pharmacokinetically enhanced amoxicillin-clavulanate 2,000/125 mg twice daily, support its use in the treatment of adult patients with community-acquired pneumonia.

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