Pharmacokinetically enhanced amoxicillin/clavulanate (2,000/125 mg) in acute bacterial rhinosinusitis caused by Streptococcus pneumoniae, including penicillin-resistant strains

Jack B. Anon, MD; Berrylin Ferguson, MD; Monique Twynholm, MSc; Brian Wynne, MD; Elchonon Berkowitz, PhD; Michael D. Poole, MD, PhD

Abstract
We evaluated the efficacy of a new pharmacokinetically enhanced formulation of amoxicillin/clavulanate (2,000/125 mg) twice daily for the treatment of acute bacterial rhinosinusitis (ABRS) caused by Streptococcus pneumoniae, particularly penicillin-resistant S pneumoniae (PRSP; penicillin minimum inhibitory concentrations [MICs] ≥ 2 µg/ml). A total of 2,482 patients received study medication (safety population). Of these, 2,324 were clinically evaluable (efficacy population), and 1,156 of them had at least one pathogen isolated at screening (bacteriology population). S pneumoniae was isolated from 371 patients in the bacteriology population, including 37 with PRSP. Follow-up in the bacteriology population on days 17 through 28 revealed that amoxicillin/clavulanate therapy was successful in 345 of 371 patients with S pneumoniae infection (93.0%) and in 36 of 37 patients with PRSP infection (97.3%), including 7 of 8 patients (87.5%) whose amoxicillin/clavulanic acid MICs were 4/2 µg/ml or higher. Pharmacokinetically enhanced amoxicillin/clavulanate was generally well tolerated, as only 2.2% of patients withdrew because of adverse events. This agent represents a valuable new therapeutic option for the empiric treatment of ABRS, particularly in areas where antimicrobial-resistant pathogens (including β-lactamase–positive organisms) are prevalent, and for the treatment of patients who are at increased risk of infection with PRSP.

Introduction
Approximately 20 million cases of acute bacterial rhinosinusitis (ABRS) occur annually in the United States.1 Rhinosinusitis is the fifth most common indication for prescribed antibiotic therapy in the United States.1 In rhinosinusitis cases known to be caused by bacterial pathogens, Streptococcus pneumoniae is the most common isolate.1

Worldwide, the prevalence of resistance to penicillin by S pneumoniae is increasing. In 2001, the prevalence of penicillin-resistant S pneumoniae (PRSP; penicillin minimum inhibitory concentrations [MICs] ≥ 2 µg/ml) in the Alexander Project surveillance study was 20.4%.2 Another concern is macrolide resistance by S pneumoniae, which in the United States and several European countries is now more common than penicillin resistance.2 In recent years, the prevalence of S pneumoniae isolates resistant to multiple classes of antimicrobials has also increased.2 These circumstances pose a considerable therapeutic challenge in empiric prescribing.

Amoxicillin/clavulanate has been available in the clinic for more than 20 years. Amoxicillin is a broad-spectrum antimicrobial, and clavulanate is a β-lactamase inhibitor. The combination covers most respiratory pathogens, including S pneumoniae and the β-lactamase–producing organisms Haemophilus influenzae and Moraxella catarrhalis. However, in the United States, amoxicillin-penicillin cross-resistance has been reported in more than 20% of PRSP isolates.3 Consequently, a formulation capable of eradicating strains with reduced amoxicillin susceptibility is needed.

A new pharmacokinetically enhanced formulation of amoxicillin/clavulanate (2,000/125 mg) has been developed to eradicate strains of PRSP with amoxicillin MICs as high as 4 µg/ml. This agent is given as two 1,000/62.5-mg
bilayer tablets twice a day. One layer of each tablet contains immediate-release amoxicillin trihydrate equivalent to 562.5 mg of amoxicillin, and potassium clavulanate equivalent to 62.5 mg of clavulanic acid. The second layer contains sustained-release crystalline sodium amoxicillin equivalent to 437.5 mg of amoxicillin. This unique formulation achieves a mean serum time above MIC (T > MIC) of 49.4% of the 12-hour dosing interval for an amoxicillin MIC of 4 µg/ml. For amoxicillin/clavulanate, a serum T > MIC of 35 to 40% of the dosing interval is predictive of high bacteriologic efficacy. In an in vitro pharmacodynamic model that simulated the human pharmacokinetics of amoxicillin/clavulanate 2,000/125 mg, significant reductions in bacterial counts were achieved for S pneumoniae strains with amoxicillin MICs of 4 to 8 µg/ml. In vivo animal models simulating human pharmacokinetics, the simulated dose equivalent to this new formulation of amoxicillin/clavulanate achieved high levels of bacteriologic success against strains of S pneumoniae with amoxicillin MICs of 4 and 8 µg/ml, as predicted by the T > MIC. In this article, we present the results of a pooled efficacy analysis of amoxicillin/clavulanate 2,000/125 mg in adult patients with ABRS caused by S pneumoniae, including PRSP, from two clinical trials.

Patients and methods

Data from two multinational (U.S. and central and eastern Europe), noncomparative studies of amoxicillin/clavulanate 2,000/125 mg (given as two 1,000/62.5 mg tablets twice daily) in adult patients with ABRS were evaluated in a pooled efficacy analysis. Selected data from one of these studies were recently published.

Both studies were conducted in accordance with Good Clinical Practice Guidelines and the Declaration of Helsinki, as amended in Somerset West, Republic of South Africa, in 1996. Study protocols for each trial were approved by national, local, or institutional ethics committees or review boards as appropriate for participating centers. All patients provided written and dated informed consent prior to study entry.

Study participants. Immunocompetent adults (age ≥ 16 yr) with a diagnosis of ABRS of 3 to 28 days (for severe cases) or 7 to 28 days (mild and moderate cases) were enrolled in the trials, provided they met the inclusion criteria for the individual study in which they participated.

A diagnosis of ABRS was based on a current history of purulent nasal discharge or purulence in the nasal cavity on examination and at least one major criterion (facial pain/pressure/tightness over the affected sinus, facial congestion/fullness, or nasal obstruction/blockage) or at least two minor criteria (nonvascular headache, cough, change in perception of smell, sore throat, tooth pain, earache, halitosis, periorbital swelling, and fever). Radiologically confirmed (Waters’ view sinus x-ray or computed tomography) rhinosinusitis within 72 hours prior to the study was also required. For inclusion in the study, patients had to consent to initial sinus puncture. A repeat sinus puncture was to be performed if clinical symptoms indicated treatment failure or if symptoms recurred. Patients had to be suitable for oral therapy and willing and able to comply with the study protocol. All women of child-bearing potential had to have a negative urine pregnancy test before study entry. These women also had to agree to the use of adequate birth control measures during the study period.

Patients were excluded from the studies if (1) they had a known or suspected hypersensitivity to study medications or related drugs, (2) they had a history of amoxicillin/clavulanate-associated cholestatic jaundice or hepatic dysfunction, (3) they had previously experienced a reaction to study medications or related drugs, (4) they had received antibacterial therapy within 7 days before study entry, (5) they were participating in another clinical trial, or (6) they had received any investigational drug or device within 30 days or within 5 half-lives of the investigational drug prior to the first dose of study medication. Patients who had previously enrolled in any study of amoxicillin/clavulanate 2,000/125 mg were excluded. Patients who had received antibacterials as prophylaxis for any other indication within 7 days prior to enrollment were not excluded, provided that this prophylaxis was discontinued at study entry. Patients with a disease or medical condition that would contraindicate treatment with study medications, including known or suspected renal or liver impairment, were also excluded, as were those who had a life-threatening or serious underlying disease likely to affect evaluation of study treatment efficacy. Other exclusion criteria were (1) the presence of any disease or intraorbital or intracranial complications that would interfere with diagnosis or evaluation of study medication efficacy, (2) a history of endoscopic sinus surgery within 6 months prior to study entry, (3) a history of chronic rhinosinusitis, and (4) the presence of nasal polyp disease extending proximal to the middle turbinate. Also excluded were (1) patients who had taken prohibited concomitant medications (e.g., tubular secretion inhibitors or corticosteroids > 10 mg/day prednisone equivalent), (2) patients who were active alcohol or drug abusers, and (3) patients who required hospitalization or parenteral antibacterial therapy. Pregnancy, lactation, and inadequate birth control were reasons to disqualify female candidates.

Study populations. The safety populations in both studies included all patients who had received at least one dose of study medication. The efficacy population consisted of all patients in the safety population who were clinically evaluable and for whom efficacy results could be verified. The bacteriology population was a subset of the efficacy population and included all patients who had at least one
The primary population of interest was the bacteriology population.

Bacteriologic assessment. Bacteriologic assessments were carried out at study entry and, when possible, at the end of therapy and the end of follow-up; in some patients, assessments were made at the time of treatment failure or upon recurrence of symptoms. Pathogens were isolated from sinus samples obtained via antral puncture.

Quantitative culture, identification, and susceptibility testing were performed at central laboratories. MICs were determined using broth microdilution for aerobic pathogens, according to National Committee for Clinical Laboratory Standards (NCCLS) guidelines. Isolates were classified as susceptible, intermediate, or resistant based on NCCLS interpretative breakpoints. NCCLS breakpoints do not yet exist for amoxicillin/clavulanate 2,000/125 mg; therefore, susceptibility to this agent was based on breakpoints for established formulations.

Efficacy assessments. Following enrollment, patients were required to attend three clinic visits: an on-therapy visit (day 2 to 10), an end-of-therapy visit (day 11 to 16), and a follow-up visit (day 17 to 28).

For the purposes of this pooled efficacy analysis, success for patients in the bacteriology population was defined as eradication of the infecting pathogen or, in the absence of an evaluable repeat sinus culture, clinical evidence of eradication (sufficient improvement in the signs and symptoms of ABRS recorded at screening such that no additional antibacterial therapy was indicated). Failure was defined as persistence of the initial pathogen (i.e., the pathogen was persistent in an evaluable repeat sinus culture) or presumed persistence of the infecting pathogen at the end of-therapy visit (i.e., an evaluable repeat sinus culture was absent and the patient had clinical signs or symptoms of ABRS necessitating further antimicrobial therapy). At the primary endpoint (follow-up visit), failure was defined as (1) recurrence in an evaluable sinus culture of the initial pathogen that was eradicated or presumed eradicated at the end-of-therapy visit or (2) clinical evidence of recurrence of the initial pathogen in the absence of a repeat sinus culture. A failure recorded at the end-of-therapy visit was carried forward to the follow-up visit. The patient’s bacteriologic response was based on the bacteriologic outcome for each pathogen identified at screening.

For each study population, 95% confidence intervals (CIs) were calculated for the success rates using exact methodology.

Safety assessment. Adverse events were recorded at the on-therapy visit and for as long as 30 days post-therapy. Adverse events were defined as any untoward medical occurrence in patients receiving study medication, but they did not necessarily have to be related to study medication. Anticipated day-to-day fluctuations in preexisting conditions—including the condition under investigation, signs and symptoms, or expected progression of the disease under investigation—were not considered adverse events unless they represented a significant worsening of the condition. All adverse events were recorded using the Medical Dictionary for Regulatory Activities Terminology (MedDRA) by body system and preferred term.

A serious adverse event was any event that was fatal, life-threatening, or permanently or temporarily incapacitating or disabling, or that resulted in hospitalization. Elective surgery and routine clinical procedures requiring hospitalization were not disqualifying, provided that they were completed without complication and not carried out as a result of an adverse event. Any event that prolonged a hospital stay or was associated with congenital anomaly, cancer, overdose (accidental or intentional), or pregnancy was also considered a serious adverse event. Additionally, any event that the investigator considered to be serious or that suggested a significant hazard, contraindication, side effect, or precaution possibly related to study medication was recorded as serious.

The severity of each adverse event and its relationship to study medication were assessed by the investigator. Patients who withdrew early from the study or who were considered clinical failures underwent a safety assessment when they left the study.

Results

Patient disposition and demographics. A total of 2,482 patients were included in the safety population. Of these, 2,324 were included in the efficacy population. In both studies, most patients were female and white (table).

Baseline bacteriology. A total of 1,379 pathogens were isolated from 1,156 patients at screening (bacteriology population). The most frequently isolated pathogen was S pneumoniae, which was isolated from 371 patients in the bacteriology population. Among this population, 37 patients (10.0%) had a total of 37 isolates of PRSP. A total of 73 (19.7%) S pneumoniae isolates in the bacteriology population at screening were resistant to erythromycin (erythromycin MICs: ≥ 1 µg/ml).

Of the S pneumoniae isolates, 5 (1.3%) had amoxicillin/clavulanate MICs of 4/2 µg/ml and another 3 (0.8%) had amoxicillin/clavulanate MICs of 8/4 µg/ml.

Efficacy. Among the 37 patients with S pneumoniae at follow-up, amoxicillin/clavulanate was successful in 345 (93.0%; 95% CI: 89.9 to 95.4) (figure). Among the 37 patients with PRSP infection, the drug was successful in 36 (97.3%; 95% CI: 85.8 to 99.9). The drug was also successful in 7 of 8 patients (87.5%) with elevated amoxicillin/clavulanate MICs, including 4 of 5 patients with MICs of 4/2 µg/ml and 3 of 3 with MICs of 8/4 µg/ml.

S pneumoniae treatment failures. Of the 371 patients with S pneumoniae infection, 26 (7.0%) were considered to be treatment failures at follow-up. Most of these patients...
did not undergo repeat sinus puncture at follow-up, and therefore bacterial infection was presumed to be persistent or recurrent based on clinical assessment. One patient was considered a clinical failure even though eradication of \textit{S} \textit{pneumoniae} was confirmed. Two other patients were classified as failures based on radiologic results, and another on the basis of radiologic results, clinical symptoms, and a presumed recurrence of \textit{S} \textit{pneumoniae} infection. \textit{S} \textit{pneumoniae} was eradicated in 2 other patients who were classified as treatment failures, but 1 patient then experienced a recurrence of \textit{Escherichia coli} infection and the other experienced a recurrence of clinical symptoms and a new infection with \textit{M} \textit{catarrhalis}. None of the \textit{S} \textit{pneumoniae} isolated from these patients was penicillin-resistant, with the exception of the 1 patient who was classified a treatment failure on the basis of radiologic results. Safety. During the on-therapy period and within 30 days post-therapy, 933 of the 2,482 patients (37.6%) in the safety population experienced at least one adverse event. The most common was diarrhea, which was reported by 409 patients (16.5%); most of these cases were mild to moderate in intensity. The only other adverse events to occur in more than 2% of patients were 74 cases of genital moniliasis (3.0%) and 59 cases of nausea (2.4%). The withdrawal rate was low, as only 54 patients (2.2%) dropped out because of any adverse event. Nine patients (0.4%) experienced at least one serious adverse event. No deaths occurred during the on-therapy period or within 30 days after the cessation of therapy.

Discussion

A pooled efficacy analysis provides a means to evaluate the efficacy of a drug against larger numbers of resistant pathogens than could be found in any individual clinical trial. In the two studies included in this analysis, 37 cases of PRSP (10.0% of all \textit{S} \textit{pneumoniae} cases) were identified. Eight patients with PRSP (21.6% of PRSP patients and 2.2% of all \textit{S} \textit{pneumoniae} patients) had amoxicillin/clavulanic acid MICs of 4/2 µg/ml or higher. Although the percentage of PRSP isolates in this study was lower than what was found in the United States in the Alexander Project surveillance (25%), it was slightly higher than the prevalence that was found in Eastern Europe (7.8%). The relatively low percentage of PRSP recovered in the pooled studies may reflect the design of the individual trials included in the analysis. For example, recent antimicrobial use and immunodeficiency are both risk factors for infection with PRSP, and such patients would have been excluded from the individual clinical trials. Also, some study centers might have been located in areas of lower resistance than the centers included in the Alexander Project, and this might have contributed to this difference.

In our analysis, pharmacokinetically enhanced amoxicillin/clavulanate 2,000/125 mg demonstrated high rates of
success in patients with ABRS caused by S pneumoniae (93.0% of the bacteriology population), including 97.3% of patients with PRSP infection and 87.5% of patients with elevated amoxicillin/clavulanic acid MICs. These high rates of success are consistent with results obtained with amoxicillin/clavulanate 2,000/125 mg in in vitro pharmacokinetic studies and in vivo animal studies that simulated the human pharmacokinetics of amoxicillin/clavulanate 2,000/125 mg. 7-8 In both in vitro and in vivo studies, amoxicillin/clavulanate 2,000/125 mg demonstrated high bactericidal activity against S pneumoniae, including strains with amoxicillin/clavulanic acid MICs of 4/2 and 8/4 µg/ml. 7-8

Bacterial eradication is believed to play a key role in maximizing clinical outcomes in respiratory tract infections, and it may help reduce the spread of antimicrobial-resistant organisms. 11 It is important that the antimicrobials selected for empiric therapy of ABRS have been documented as efficacious against the likely infecting organisms. 12 As the results of our analysis demonstrate, amoxicillin/clavulanate 2,000/125 mg is highly effective against S pneumoniae, the most common pathogen isolated in patients with ABRS. The combination of amoxicillin and the β-lactamase inhibitor clavulanate also makes it a suitable antimicrobial for infections caused by H influenzae and by M catarrhalis.

In addition to efficacy, safety and tolerability need to be taken into account when prescribing. Amoxicillin/clavulanate has been clinically available for more than 20 years and has an established safety profile. 13,14 The safety profile of the 2,000/125-mg formulation has been shown to be similar to that of conventional formulations. 15,16 In the two studies included in our analysis, the combination was well tolerated, and few patients withdrew from studies because of adverse events.

This new formulation of amoxicillin/clavulanate provides a valuable treatment option for the empiric therapy of ABRS, particularly in areas where antimicrobial-resistant (including β-lactamase–positive) pathogens are prevalent, and in patients who are at increased risk of infection with PRSP.

Acknowledgments
The authors thank the members of the 551 and 592 clinical study groups. Statistical design and analysis were provided by S. Miller, C. Blackburn, N. Bunday, K. Lewis, T. Pullan, and V. Winfield.

References