Pharmacodynamic Analysis and Clinical Trial of Amoxicillin Sprinkle Administered Once Daily for 7 Days Compared to Penicillin V Potassium Administered Four Times Daily for 10 Days in the Treatment of Tonsillopharyngitis Due to *Streptococcus pyogenes* in Children

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An a priori pharmacokinetic/pharmacodynamic (PK/PD) target of 40% daily time above the MIC (T > MIC; based on the MIC\textsubscript{90} of 0.06 \(\mu\)g/ml for *Streptococcus pyogenes* reported in the literature) was shown to be achievable in a phase 1 study of 23 children with a once-daily (QD) modified-release, multiparticulate formulation of amoxicillin (amoxicillin sprinkle). The daily T > MIC achieved with the QD amoxicillin sprinkle formulation was comparable to that achieved with a four-times-daily (QID) penicillin VK suspension. An investigator-blinded, randomized, parallel-group, multicenter study involving 579 children 6 months to 12 years old with acute streptococcal tonsillopharyngitis was then undertaken. Children were randomly assigned 1:1 to receive either the amoxicillin sprinkle (475 mg for ages 6 months to 4 years, 775 mg for ages 5 to 12 years) QD for 7 days or 10 mg/kg of body weight of penicillin VK QID for 10 days (up to the maximum dose of 250 mg QID). Unexpectedly, the rates of bacteriological eradication at the test of cure were 65.3% (132/202) for the amoxicillin sprinkle and 68.0% (132/194) for penicillin VK (95% confidence interval, −12.0% to 6.6%). Thus, neither antibiotic regimen met the minimum criterion of ≥85% eradication ordinarily required by the U.S. FDA for first-line treatment of tonsillopharyngitis due to *S. pyogenes*. The results of subgroup analyses across demographic characteristics and current infection characteristics and by age/weight categories were consistent with the primary-efficacy result. The clinical cure rates for amoxicillin sprinkle and penicillin VK were 86.1% (216/251) and 91.9% (204/222), respectively (95% confidence interval, −11.6% to −0.4%). The results of a post hoc PD analysis suggested that a requirement for 60% daily T > MIC\textsubscript{90} more accurately predicted the observed high failure rates for bacteriologic eradication with the amoxicillin sprinkle and penicillin VK suspension studied. Based on the association between longer treatment courses and maximal bacterial eradication rates reported in the literature, an alternative composite PK/PD target taking into consideration the duration of therapy, or total T > MIC, was considered and provides an alternative explanation for the observed failure rate of amoxicillin sprinkle.

*Streptococcus pyogenes* accounts for approximately 5% to 10% of all pharyngitis cases in adults and 15% to 30% in children, with a peak incidence of infection in persons 5 to 15 years of age (19). Penicillin has long been the drug of choice for the treatment of streptococcal pharyngitis (2). Despite the development of resistance among respiratory bacterial pathogens, *S. pyogenes* remains uniformly sensitive to penicillin and ampicillin (28).

Amoxicillin is an accepted alternative to penicillin for the eradication of *S. pyogenes* due to its well-established safety, efficacy, and narrow spectrum of activity (2, 35). Amoxicillin is the most commonly prescribed antibiotic for the treatment of pharyngitis in the United States (27). Immediate-release amoxicillin is not approved for once-daily (QD) dosing. Two small studies and one larger, more recently conducted, single-center study have evaluated the efficacy of immediate-release amoxicillin suspension for 10 days. Two studies found the efficacy to be equivalent to that of 10 days of penicillin V (three times daily [TID] or four times daily [QID]) (16, 38), and one study found QD amoxicillin noninferior to amoxicillin two times daily (BID) for 10 days (7). Two studies have reported on the use of a shorter course of amoxicillin as a treatment for *S. pyogenes* tonsillopharyngitis, one in children (8) and one in adults (33). In these studies, immediate-release amoxicillin suspension and tablets administered BID for 6 days were found to be as effective as 10 days of penicillin V administered TID (8, 33). However, limitations in these study designs preclude definitive conclusions.

This paper describes a phase 1 pharmacokinetic (PK) study of children that assessed the single-dose administration of an investigational oral amoxicillin sprinkle designed to sequentially deliver an immediate-release and multiple delayed-re-
lease pulses of amoxicillin to provide prolonged plasma concentrations of amoxicillin, thereby enabling QD dosing, relative to the administration of immediate-release amoxicillin. Based on a PK/pharmacodynamics (PD) assessment of this phase 1 data and PK data for an oral penicillin VK suspension in the literature, a clinical trial was completed comparing the amoxicillin suspension administered QD for 7 days to penicillin VK QID for 10 days in children with tonsillopharyngitis secondary to S. pyogenes.

**MATERIALS AND METHODS**

**PD assessment.** Although a daily time above the MIC (T > MIC) target for amoxicillin or penicillin against S. pyogenes has not been clearly defined, a target 40% T > MIC for beta-lactam antibiotics has been established for many drug-microbe combinations (5, 9). Therefore, an a priori PD target of 40% daily T > MIC (assuming a MIC of 0.06 μg/ml for S. pyogenes, based on reports in the literature [28]) for unbound drug in plasma (amoxicillin unbound fraction, 82% [47], and penicillin VK unbound fraction, 45% [29]) was selected. PD assessments were made for both dose response and amoxicillin (peak and trough) and for the penicillin VK regimen. PK data from a phase 1 study following a single dose of amoxicillin and PK data for penicillin VK from published literature (17) were utilized to calculate the daily T > MIC for the regimen. The phase 1 study used a 475-mg amoxicillin suspension for the control conditions for children 6 months to 12 years old with an upper respiratory tract infection.

After the results of the clinical trial were available, daily T > MICs were recalculated using the MIC values determined from the results for the baseline S. pyogenes isolates in the clinical trial (0.015 μg/ml) (Table 1). A further PD analysis was then performed which involved fitting the daily T > MIC data for amoxicillin, from the population of subjects in the above-referenced phase 1 study to a log normal distribution and determining the log normal distribution parameters and 95% confidence intervals (using JMP version 5.0.1a). The cumulative distribution of the fitted T > MIC data was then utilized to determine the projected number of therapeutic failures, using the PD target of 40% daily T > MIC, and comparing this to the actual number of failures observed in the clinical trial. The observed number of subjects failing treatment in the clinical trial was then evaluated in relation to the same cumulative T > MIC distribution to determine the theoretical minimum daily T > MIC required to achieve successful eradication of S. pyogenes (i.e., the efficacy cutoff).

**Clinical trial design.** This was an investigator-blinded, randomized, parallel-group, multicenter clinical study involving children with acute streptococcal tonsillitis/pharyngitis. There were four study visits for bacteriological and/or clinical assessments: (i) modified intent to treat (mITT), all patients who received at least one dose of study drug and who had at least one postbaseline clinical safety assessment; (ii) modified intent to treat (mITT), all ITT/safety patients with a baseline throat swab culture that was positive for S. pyogenes; (iii) per-protocol clinical (PPc), all ITT/safety patients with either a rapid streptococcus A test at baseline or a baseline throat swab culture that was positive for S. pyogenes, excluding those with major protocol violations and those that do not have a clinical assessment at the TOC visit; and (iv) per-protocol bacteriological (PPb), the primary efficacy population, which consisted of all PPc patients with a baseline throat swab culture positive for S. pyogenes and with throat swab culture results available at the TOC visit. Efficacy results for clinical failures that withdrew early from the study and started a new antimicrobial for tonsillitis and/or pharyngitis due to tetracyclines and/or pharyngitis were included in the PPb analyses.

**Efficacy assessments and outcome.** The primary efficacy endpoint was the bacteriological outcome at TOC in the PPb population. Secondary efficacy endpoints included (i) bacteriological outcome at the TOC for the mITT and PPb populations; (ii) bacteriological outcome at the LPT visit for the mITT and PPb populations; (iii) clinical outcome in the ITT/safety, mITT, PPc, and PPb populations at TOC; and (iv) clinical outcome in the ITT/safety and PPc populations at LPT. A throat culture was obtained at TOC, LPT, and/or early withdrawal to confirm the presence or absence of S. pyogenes. The bacteriological response at the TOC visit was assessed using the following categories: (i) eradication, a negative throat culture for S. pyogenes at the TOC visit, irrespective of the clinical response at TOC, and no new antimicrobial therapy was started before the culture was obtained at the TOC visit; (ii) failure, a throat culture that was positive for S. pyogenes at the TOC visit, irrespective of the clinical status, and (iii) presumed failure, no culture results available at the TOC visit, but a new antimicrobial was started for tonsillitis/pharyngitis before the TOC visit.

The bacteriological response at the LPT visit was assessed using the following categories: (i) eradication, a negative throat culture for S. pyogenes at the LPT visit and a negative throat culture for S. pyogenes at LPT or no culture result at LPT but patient was a clinical cure at the LPT visit; (ii) failure, a throat culture that was positive for S. pyogenes at TOC but irrespective of the outcome at LPT; (ii) secondary failure, eradication at TOC but a throat culture that was positive for S. pyogenes with the same streptococcal strain at the LPT visit (carrier/recolonization); (iv) new infection, eradication at TOC but a culture that was positive for S. pyogenes with a different streptococcal strain at the LPT visit; and (v) presumed failure, no culture results at LPT visit but antibacterial therapy administered between the TOC and LPT visits for the treatment of tonsillitis/pharyngitis. Clinical assessments were conducted at each study visit. The investigator documented the presence or absence of the following signs and symptoms of tonsillitis/pharyngitis: sore throat, odynophagia, fever or history of fever, chills, strawberry tongue, uvular edema, pharyngeal erythema, cervical lymphadenopathy (enlargement of the periauricular, submandibular, submental, anterior and/or posterior cervical lymph nodes), and tender lymph nodes. In addition, if the sign/symptom was present, the investigator assessed the intensity as mild (except for pharyngeal erythema) or moderate (except for children or severe, with the exception of sore throat, strawberry tongue, and pharyngeal exudates, which were assessed as either present or absent according to definitions provided.

Based on the evaluation of the signs and symptoms of tonsillitis/pharyngitis, the
clinical response at the TOC and LPT visits was assessed using the following categories. (i) Cure was defined as the resolution of baseline clinical signs/symptoms and no appearance of new signs/symptoms at the TOC visit and no further antimicrobial therapy required for tonsillopharyngitis. A response of cure at LPT visit required a cure at TOC, continued resolution of baseline clinical signs/symptoms, no appearance of new signs/symptoms at the LPT visit, and no further antimicrobial therapy required for tonsillopharyngitis. (ii) Failure was defined as the persistence of baseline clinical signs/symptoms, including the appearance of new signs/symptoms or progression of the infection requiring additional antimicrobial therapy or a change in treatment regimen at the TOC visit. At the LPT visit, failure was defined as failure at TOC or the occurrence of signs/symptoms of a new infection that required the initiation of new antimicrobial therapy for the indication between the TOC and LPT visits. (iii) Indeterminate was the category assigned when circumstances, such as missing posttreatment information or early discontinuation of treatment for reasons that were not drug related, precluded classification as clinical cure or failure.

**PFGE.** Pulsed-field gel electrophoresis (PFGE) testing was performed on both the baseline and LPT visits isolates for all patients who had cultures that were positive at baseline, negative at TOC, and positive at the LPT visit for *S. pyogenes*. The PFGE testing was performed to determine if the culture isolates from the baseline and LPT visits were concordant or different using established interpretation criteria (46). Patients with discordant strains of *S. pyogenes* were determined to have persistent colonization or recurrence of the bacterial organism, whereas those patients with discordant strains of *S. pyogenes* were determined to have a new infection with a new strain of *S. pyogenes*.

**Statistical methods.** All data analyses were performed using SAS statistical software, version 8.2. All statistical tests, where considered relevant, were two sided and were interpreted at a 0.05 significance level. Patient demographic and baseline characteristics were summarized by treatment group for all study centers combined. Continuous (quantitative) variables such as age and weight were summarized using mean, standard deviation, median, minimum, and maximum, and the treatment groups were compared with respect to mean age and weight using analysis of variance with treatment group and region of the United States where enrollment occurred (Northeast, Midwest, etc.) as the main effects. Categorical (qualitative) variables, such as gender, race, ethnicity, age group, physical examination findings, clinical assessment of signs and symptoms of tonsillitis and/or pharyngitis, and number of previous episodes of tonsillopharyngitis in the previous 12 months, were summarized using frequencies and percentages, and the treatment groups were compared (if appropriate) by using a Cochran Mantel-Haenszel test.

The two treatment groups were compared with regard to compliance during the first 3 days on study medication and with regard to overall compliance during the 10-day treatment course by using a Cochran Mantel-Haenszel test for qualitative categories and by means of an analysis of variance for the summary statistics. The treatment group differences in satisfactory bacteriological outcome (i.e., bacteriological response of eradication for the PFP population and eradication or presumed eradication for other analysis populations) rates were compared by calculating a Cochran Mantel-Haenszel test estimate and two-sided 95% confidence interval for the difference in satisfactory bacteriological outcome rates. The primary efficacy analysis was performed using the PFP population. A treatment-by-region interaction (homogeneity of the odds ratio across U.S. regions) was tested using the Breslow-Day test. If an interaction existed, an exploratory analysis was to be performed to find the source of this interaction. For the secondary efficacy variables of bacteriological and clinical outcomes at the TOC and LPT visits, the tests between the two treatment groups were performed with the same analysis model as used for the primary efficacy analysis. A satisfactory bacteriological outcome of 90% in each treatment group and a maximum difference between test and standard treatments of a 5 value of 10% were assumed. These assumptions were consistent with those of other studies for the tonsillitis/pharyngitis indication. A sample size of 150 PFP patients per treatment arm was chosen to ensure with 80% power that the test treatment would be considered noninferior if the endpoint of the two-sided 95% confidence interval for the treatment difference was −10% or greater.

**RESULTS**

**PK/PD assessment.** Twenty-three children were included in the PK phase 1 trial: 11 children (6 months to 4 years old) received a 475-mg amoxicillin sprinkle in a fed state (treatment A) and 12 children (5 to 12 years old) received a 775-mg amoxicillin sprinkle in a fed state (treatment B) and a 775-mg amoxicillin sprinkle in a fasted state (treatment C). Single-dose PK parameters for 475 mg and 775 mg of amoxicillin sprinkle under fed and/or fasted conditions are presented in Table 1. Under fed conditions, relative to the MIC value of 0.06 μg/ml reported in the literature, the mean daily percentages of T >MIC were 63.8%, 58.3%, and 49.3% for 6 months to 4 years old receiving a 475-mg amoxicillin sprinkle under fed conditions (treatment A) and children 5 to 12 years old receiving a 775-mg amoxicillin sprinkle under fed (treatment B) and fasted (treatment C) conditions, respectively. Based on PK data in the literature (17), the mean daily percentage of T >MIC for 10 mg/kg of penicillin, relative to a MIC value of 0.06 μg/ml, was 41.0% under fasted conditions.

The MIC range of amoxicillin and penicillin for the 396 *S. pyogenes* strains isolated at baseline from children in the clinical trial was <0.004 to 0.012 μg/ml with a MIC for 0.015 μg/ml for both amoxicillin and penicillin, lower than the MIC value of 0.06 μg/ml reported in the literature.

The daily T >MIC was recalculated based on the MIC value determined in the clinical trial. The individual results for the 23 children in the phase 1 study for percentage of the T >MIC (using the MIC of 0.015 mg/ml) for the three treatments are shown in Fig. 1, which clearly demonstrates no trends for age, dose, or food intake with dosing. From those results, the average daily T >MIC for QD amoxicillin sprinkle was confirmed to be similar to that of QID penicillin determined from PK data in the literature (17) (Fig. 2). The daily T >MIC for both treatment regimens exceeded the target 40% daily T >MIC anticipated to be predictive of efficacy. The daily percentages of T >MIC achieved were 71.6%, 68.3%, and 59.9%, and 66.5% for the 475-mg amoxicillin sprinkle (ages 6 months to 4 years, fed state), the 775-mg amoxicillin sprinkle (ages 5 to 12 years, fed state), and the 775-mg amoxicillin sprinkle (ages 5 to 12 years, fasted state), and 10 mg/kg of penicillin VK QID, respectively.

**Clinical trial.** A total of 579 children were randomly assigned to the study medication groups (amoxicillin sprinkle, 290 patients, and penicillin VK, 289 patients). Of patients in the penicillin VK treatment group, 13.6% discontinued prior to completing the study, versus 11.1% in the amoxicillin sprinkle treatment group (Table 2).

The demographic characteristics of the two treatment groups are summarized for the ITT/safety populations in Table

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<table>
<thead>
<tr>
<th>Treatment group</th>
<th>PK parameter (unit of measure)</th>
<th>AUC&lt;sub&gt;0-24&lt;/sub&gt; (μg-hr/ml)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (μg/ml)</th>
<th>T&lt;sub&gt;max&lt;/sub&gt; (hr)</th>
<th>t&lt;sub&gt;1/2&lt;/sub&gt; (hr)</th>
<th>K&lt;sub&gt;el&lt;/sub&gt; (1/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (n = 11)</td>
<td>39.3</td>
<td>8.65</td>
<td>2.5</td>
<td>1.98</td>
<td>0.529</td>
<td></td>
</tr>
<tr>
<td>B (n = 12)</td>
<td>34.4</td>
<td>8.93</td>
<td>2</td>
<td>1.6</td>
<td>0.456</td>
<td></td>
</tr>
<tr>
<td>C (n = 12)</td>
<td>34.2</td>
<td>10.3</td>
<td>1.5</td>
<td>1.51</td>
<td>0.481</td>
<td></td>
</tr>
</tbody>
</table>

* AUC<sub>0-24</sub>, area under the concentration-time curve from 0 to the last timepoint with a measurable drug concentration; C<sub>max</sub>, maximum concentration of drug in serum; T<sub>max</sub>, time to maximum concentration of drug in serum; t<sub>1/2</sub>, half-life; K<sub>el</sub>, elimination rate constant.

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* MIC, minimum inhibitory concentration.
In the amoxicillin sprinkle ITT/safety population (n/H11005 284), 3.9% of children had received an antimicrobial within 30 days of study entry, compared to 5.7% in the penicillin VK population (n/H11005 282) (P/H11005 0.33). The number of episodes of tonsillopharyngitis in the 12 months prior to study entry was zero in 68.3% of the amoxicillin sprinkle group and 63.8% of the penicillin VK group (P/H11005 0.49). The percentages of subjects experiencing one, two, or three episodes of tonsillopharyngitis in the prior 12 months for the amoxicillin sprinkle population FIG. 1. Plot of percentages of $T >$MIC for individual subjects versus sequence number. Daily $T >$MIC for amoxicillin sprinkle QD was determined for individual subjects from a phase 1 study in pediatric patients with upper respiratory tract infections and was based on the MIC$_{95}$ (0.015 $\mu g$/ml) determined in the phase 3 clinical trial. The numbers of children receiving amoxicillin sprinkle were as follows: 6 months to 4 years old, 475 mg, fed, n = 11; 5 to 12 years old, 775 mg, fed, n = 12; 5 to 12 years old, 775 mg, fasted, n = 12.

3. In the amoxicillin sprinkle ITT/safety population (n = 284), 3.9% of children had received an antimicrobial within 30 days of study entry, compared to 5.7% in the penicillin VK population (n = 282) (P = 0.33). The number of episodes of tonsillopharyngitis in the 12 months prior to study entry was zero in 68.3% of the amoxicillin sprinkle group and 63.8% of the penicillin VK group (P = 0.49). The percentages of subjects experiencing one, two, or three episodes of tonsillopharyngitis in the prior 12 months for the amoxicillin sprinkle population.

3. In the amoxicillin sprinkle ITT/safety population (n = 284), 3.9% of children had received an antimicrobial within 30 days of study entry, compared to 5.7% in the penicillin VK population (n = 282) (P = 0.33). The number of episodes of tonsillopharyngitis in the 12 months prior to study entry was zero in 68.3% of the amoxicillin sprinkle group and 63.8% of the penicillin VK group (P = 0.49). The percentages of subjects experiencing one, two, or three episodes of tonsillopharyngitis in the prior 12 months for the amoxicillin sprinkle population.

**TABLE 2. Patient disposition**

<table>
<thead>
<tr>
<th>Disposition, reason</th>
<th>No. of patients (%) receiving or discontinuing treatment</th>
<th>Amoxicillin sprinkle</th>
<th>Penicillin VK</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized group assignment</td>
<td>290 (100.0)</td>
<td>289 (100.0)</td>
<td>579 (100.0)</td>
<td></td>
</tr>
<tr>
<td>Completed study</td>
<td>287 (100.0)</td>
<td>287 (100.0)</td>
<td>574 (100.0)</td>
<td></td>
</tr>
<tr>
<td>Prematurely discontinued study</td>
<td>32 (11.1)</td>
<td>39 (13.6)</td>
<td>71 (12.4)</td>
<td></td>
</tr>
<tr>
<td>Reason for premature discontinuation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insufficient therapeutic effect</td>
<td>13 (4.5)</td>
<td>8 (2.8)</td>
<td>21 (3.7)</td>
<td></td>
</tr>
<tr>
<td>Adverse event</td>
<td>13 (4.5)</td>
<td>11 (3.8)</td>
<td>24 (4.2)</td>
<td></td>
</tr>
<tr>
<td>Patient lost to follow-up</td>
<td>4 (1.4)</td>
<td>7 (2.4)</td>
<td>11 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Consent withdrawn</td>
<td>2 (0.7)</td>
<td>8 (2.8)</td>
<td>10 (1.7)</td>
<td></td>
</tr>
<tr>
<td>Patient noncompliance</td>
<td>0 (0.0)</td>
<td>2 (0.7)</td>
<td>2 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Protocol violations</td>
<td>0 (0.0)</td>
<td>1 (0.3)</td>
<td>1 (0.2)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0 (0.0)</td>
<td>2 (0.7)</td>
<td>2 (0.3)</td>
<td></td>
</tr>
</tbody>
</table>
were 19%, 7.7%, and 3.2% and for the penicillin VK group were 22%, 8.9%, and 3.9%, respectively.

The baseline characteristics of the infections are summarized in Table 4. There were no significant differences between the two treatment groups in the occurrence of previous tonsillitis or antimicrobial therapy or in the distribution of characteristics of the current infection for the ITT/safety population.

In the ITT/safety population, 97.2% of patients in the amoxicillin sprinkle group and 98.9% in the penicillin VK group were 100% compliant with their study medication during the first 3 days of the study. Over the entire treatment period, 80.4% of patients in the amoxicillin sprinkle group and 90.4% of patients in the penicillin VK group were equally represented.

The results of the secondary efficacy analysis of bacteriological outcome at the LPT in the PPb population are presented in Table 5. The total bacteriologic failures at TOC plus LPT visits were 43.6% for amoxicillin sprinkle and 40.3% for penicillin VK.

**Clinical outcome.** The results of the secondary efficacy analysis of clinical outcome at the TOC visit in the PPc population are presented in Table 5. As observed for the bacteriological efficacy analyses, amoxicillin sprinkle QD for 7 days failed to demonstrate noninferiority to penicillin VK QID for 10 days at TOC (95% confidence interval, −11.6% to −0.4%).

**PFGE testing.** Twenty-three PPb patients (amoxicillin sprinkle, 11, and penicillin VK, 12) were found to have cultures that were positive at baseline, negative at TOC, and positive at the LPT visit for *S. pyogenes*. PFGE testing was performed to determine if the isolates from these patients at the baseline and LPT visits were concordant or discordant strains of *S. pyogenes*. Seventeen of 23 (75%) patients (amoxicillin sprinkle, 9, and penicillin VK, 8) were determined to have concordant (antimicrobial therapies within 30 days of study entry, *S. pyogenes* infections within 12 months of study entry, and current infection signs and symptoms) characteristics. In general, the rate of satisfactory bacteriological outcome at the TOC visit across demographic characteristics and current infection characteristics was consistent with the outcome at the TOC visit for the primary efficacy population (i.e., the overall PPb population), although not all categories within a subgroup were equally represented.
TABLE 5. Bacteriological outcomes at the TOC visit in PPb population and clinical outcomes at TOC visit in PPc population

<table>
<thead>
<tr>
<th>Efficacy endpoint and outcome</th>
<th>No. (%) of patients treated with</th>
<th>Amoxicillin sprinkle</th>
<th>Penicillin VK</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacteriological outcome at TOC</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. in population</td>
<td>202 (100)</td>
<td>194 (100)</td>
<td></td>
</tr>
<tr>
<td>Eradication</td>
<td>132 (65.3)</td>
<td>132 (68.0)</td>
<td></td>
</tr>
<tr>
<td>Total failures</td>
<td>70 (34.7)</td>
<td>62 (32.0)</td>
<td></td>
</tr>
<tr>
<td>Failure due to persistence</td>
<td>59 (29.2)</td>
<td>56 (28.9)</td>
<td></td>
</tr>
<tr>
<td>Presumed failurea</td>
<td>11 (5.4)</td>
<td>6 (3.1)</td>
<td></td>
</tr>
<tr>
<td><strong>Bacteriological outcome at LPT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. in population</td>
<td>195 (100)</td>
<td>181 (100)</td>
<td></td>
</tr>
<tr>
<td>Eradication at TOC and at LPTb</td>
<td>108 (55.4)</td>
<td>103 (56.9)</td>
<td></td>
</tr>
<tr>
<td>Total failures at LPT visits</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failure at TOCc</td>
<td>68 (34.9)</td>
<td>58 (32.0)</td>
<td></td>
</tr>
<tr>
<td>Presumed failured</td>
<td>8 (4.1)</td>
<td>7 (3.9)</td>
<td></td>
</tr>
<tr>
<td>Eradication at LPT with failure at LPT, same strain</td>
<td>9 (4.6)</td>
<td>9 (4.4)</td>
<td></td>
</tr>
<tr>
<td>New infection at LPTe</td>
<td>2 (1.0)</td>
<td>4 (2.2)</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical outcome at TOC</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. in population</td>
<td>251 (100)</td>
<td>222 (100)</td>
<td></td>
</tr>
<tr>
<td>Clinical cure</td>
<td>216 (86.1)</td>
<td>204 (91.9)</td>
<td></td>
</tr>
<tr>
<td>Clinical failure</td>
<td>30 (12.0)</td>
<td>14 (6.3)</td>
<td></td>
</tr>
<tr>
<td>Indeterminate</td>
<td>5 (2.0)</td>
<td>4 (1.8)</td>
<td></td>
</tr>
</tbody>
</table>

a Presumed failures included those patients who started a new antimicrobial for the treatment of tonsillitis and/or pharyngitis before the TOC visit.

b Presumed failures included those with a bacteriological response of eradication at TOC and presumed eradication at LPT.

c Failure at TOC was carried forward as a failure at LPT.

d Presumed failures included those patients who started a new antimicrobial for the treatment of tonsillitis and/or pharyngitis between the TOC and LPT visit.

e One subject in the penicillin VK group is included in this outcome although no PFGE was performed.

**DISCUSSION**

Based on a phase 1 PK/PD analysis, the amoxicillin sprinkle and penicillin VK treatment regimens used in this study were predicted to exceed a 40% target daily T > MIC coverage against *S. pyogenes*. However, in a clinical trial, neither the amoxicillin sprinkle administered QD for 7 days nor penicillin VK QID for 10 days met the minimum U.S. FDA criterion of ≥85% bacteriological eradication at TOC ordinarily required for first-line therapy (48). In fact, the rates of satisfactory bacteriological outcome in the amoxicillin sprinkle and penicillin VK treatment groups were 65.3% and 68.0%, respectively, corroborating literature reports of a trend to increasing rates of failure of penicillin in children (6). Because the failure to achieve the a priori PK/PD drug attainment target could not explain the low bacteriological eradication rates observed for amoxicillin sprinkle QD and penicillin VK QID in the clinical trial, alternative PK/PD modeling was undertaken. One analysis suggested that a requirement for 60% daily T > MIC more closely fit the observed results in the clinical trial.

Another alternative PK/PD target explored was total T > MIC, a composite parameter based on the overall T > MIC achieved over the duration of therapy. This alternative approach is supported by a review (15) that emphasized the importance of the aggregate time penicillin remains at effective bactericidal levels. We evaluated this alternative model and found that it suggested that the amoxicillin sprinkle failure rate might be explainable, since the dosing regimen of 475-mg amoxicillin sprinkle QD for 7 days and 775-mg amoxicillin sprinkle QD for 7 days provided 5.0 and 4.8 days of total T > MIC, respectively, while the model suggested a need for 6.7 days to achieve an eradication rate of 85%. However, this alternative total T > MIC model did not predict the observed penicillin failure rate; penicillin QID for 10 days achieved a total T > MIC of 6.6 days.

We considered using tonsillar antibiotic levels rather than plasma levels of drug in our model; however, there is limited
literature available on amoxicillin concentrations in tonsillar tissue. The data presented generally describe tonsillar tissue concentrations from tissue biopsy homogenates, which underestimate the interstitial-tissue concentrations of amoxicillin. Beta-lactams are known to distribute almost exclusively from

FIG. 3. PD endpoint assessment of projected failures based on different percentage of $T > \text{MIC}$ PD endpoints (using phase 1 data) using unbound drug at a MIC of 0.015 $\mu$g/ml. The daily $T > \text{MIC}$ data for amoxicillin sprinkle from a separate phase 1 study were fitted to a log normal distribution, and the log normal distribution parameters and 95% confidence intervals were determined (using JMP version 5.0.1a). The cumulative distribution of the fitted $T > \text{MIC}$ data was then utilized to determine the projected number of therapeutic failures assuming a 40% $T > \text{MIC}$. The scale parameter estimate was 4.17, with a 95% confidence interval of 4.08 to 4.25. The shape parameter estimate was 0.25, with a 95% confidence interval of 0.21 to 0.31.

FIG. 4. Plot of eradication rate versus $T > \text{MIC}$ (assuming a MIC$_{95}$ of 0.015 $\mu$g/ml) achieved over the duration of therapy, i.e., total $T > \text{MIC}$, for various penicillin (Pen VK) dose regimens (▲) (4, 11, 12, 13, 14, 16, 18, 20, 21, 22, 23, 24, 25, 26, 30, 31, 32, 34, 37, 38, 39, 40, 41, 42, 43, 44, 45, 49, 50) compared to those achieved by amoxicillin sprinkle ( ■ with 95% confidence interval shown as a bar) (based on average of both doses) and various amoxicillin dose regimens ( ●) (1, 8, 11, 16, 33, 38) for the treatment of tonsillopharyngitis due to $S$. pyogenes. Model fit is based on penicillin VK data. The dashed line is at 85% eradication per U.S. FDA criterion standard.

FIG. 5. Total $T > \text{MIC}$ (days) was based on the MIC$_{95}$ of 0.015 $\mu$g/ml from the clinical trial and unbound-drug concentrations in plasma. Total $T > \text{MIC}$ for amoxicillin sprinkle QD for 7 days was determined from the results of a phase 1 study in pediatric patients with upper respiratory tract infections. Total $T > \text{MIC}$ for penicillin (Pen VK) QID for 10 days was based on data in the literature (17). The number of children receiving amoxicillin sprinkle were as follows: 6 months to 4 years old, 475 mg, fed, $n = 11$; 5 to 12 years old, 775 mg, fed, $n = 12$; 5 to 12 years old, 775 mg, fasted, $n = 12$. Values displayed are the means ± standard deviations of the results.
plasma into the interstitial-space fluid of well-perfused tissues due to their hydrophilic properties. This is especially so for compounds with low protein binding, such as amoxicillin (the protein-bound fraction is 22%). Furthermore, it is the free, unbound drug that distributes into the interstitial spaces and exerts antimicrobial activity. Thus, amoxicillin concentrations in the interstitial spaces of the tonsillar tissue are expected to be similar to plasma concentrations of amoxicillin not bound by plasma protein; the unbound plasma concentration of amoxicillin is considered a adequate representation of expected amoxicillin exposure in the interstitial spaces of the tonsillar tissue.

The American Academy of Pediatrics Committee on Infectious Diseases recently stated that preliminary investigations suggest that orally administered amoxicillin given as a single daily dose for 10 days is an antibiotic regimen with an effectiveness comparable to that of orally administered penicillin VK given TID for 10 days (35). If confirmed by additional investigations, QD amoxicillin could become an alternative regimen for the treatment of streptococcal tonsillitis. This assessment was based on the results of two small studies reporting that a QD dose of immediate-release amoxicillin (50 mg/kg QD to a maximum 750 mg QD) for 10 days was as effective in the eradication of \(S. \text{pyogenes}\) as penicillin V TID or QID for 10 days. (16, 38) However, the small number of patients in each of those studies (80 or fewer patients per treatment group in each study) precluded definitive conclusions. In another, more recently published study, the noninferiority of immediate-release amoxicillin QD (750 mg QD for subjects <40 kg or 1,000 mg QD for subjects ≥40 kg) compared to immediate-release amoxicillin BID (375 mg BID for subjects <40 kg or 500 mg BID for subjects ≥40 kg) for 10 days was assessed. In that larger, investigator-blinded, single-center study (7), the reported bacteriological failure rates were 20.1% and 15.5% following treatment with amoxicillin QD and BID regimens, respectively, demonstrating higher failure rates than acceptable under current U.S. FDA standards for first-line therapy.

For the amoxicillin sprinkle QD regimen studied here and based on total \(T \geq \text{MIC}\) considerations, it may be that the bacteriological eradication rate would have been higher following 10 days of therapy rather than the 7 days used. Amoxicillin sprinkle was designed to provide plasma concentrations of amoxicillin that were prolonged relative to the plasma concentrations with immediate-release amoxicillin. The predicted total \(T \geq \text{MICs}\) (assuming a MIC\(_{90}\) of 0.015 \(\mu\)g/ml) for the 475-mg and 775-mg amoxicillin doses for 10 days are 7.2 and 6.8 days, respectively, exceeding the total \(T \geq \text{MIC}\) target of 6.7 days required for an eradication rate of 85% as suggested by the alternative total \(T \geq \text{MIC}\) model (Fig. 4). The total \(T \geq \text{MIC}\) expected to be achieved by amoxicillin sprinkle QD for 10 days is greater than that which would be achieved by the QD administration of 750 mg of immediate-release amoxicillin in the results of studies previously described, and thus, amoxicillin sprinkle QD for 10 days would be expected to have a higher eradication rate than that reported in the literature for 750 mg of immediate-release amoxicillin QD for 10 days. The results of recently completed studies of a QD modified-release amoxicillin tablet formulation, similar to the amoxicillin sprinkle formulation studied here, in the treatment of tonsillogynitis secondary to \(S. \text{pyogenes}\) in adolescents and adults lend credence to the importance of duration of therapy and total \(T \geq \text{MIC}\) achieved by the modified-release amoxicillin formulations.

A 7-day treatment course with the 775-mg amoxicillin tablet QD failed to demonstrate noninferiority to 250 mg of penicillin VK QID for 10 days. However, in the results of a second study, a 775-mg amoxicillin tablet QD for 10 days was noninferior to 250 mg of penicillin VK QID for 10 days (amoxicillin tablet eradication rate, 85.0%; and penicillin VK eradication rate, 83.4%) (3).

In summary, neither this amoxicillin sprinkle formulation administered QD for 7 days nor 10 mg/kg of penicillin VK suspension QID for 10 days meet the minimum criterion of ≥85% eradication rate ordinarily required by the U.S. FDA for first-line treatment of tonsillopharyngitis due to \(S. \text{pyogenes}\). A daily \(T \geq \text{MIC}\) of 40% for the dosing interval, widely accepted as a relevant PD endpoint, was achieved with both drug regimens, and yet both regimens produced unsatisfactory eradication rates.

Considering daily \(T \geq \text{MIC}\) in isolation, an alternative PK/PD target of 60% daily \(T \geq \text{MIC}\) more closely predicted the results in the clinical trial and described in the literature for eradication of \(S. \text{pyogenes}\) with penicillin and amoxicillin in the pediatric population. The effect of total \(T \geq \text{MIC}\) achieved for the duration of therapy was also considered and would appear to be an important contributor to the efficacies of penicillin and amoxicillin in terms of bacterial eradication.

REFERENCES


31. Reference deleted.


