Original article

Pharmacokinetic/pharmacodynamic evaluation of amoxicillin, amoxicillin/clavulanate and ceftriaxone in the treatment of paediatric acute otitis media in Spain

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\textbf{Abstract}

\textbf{Introduction: }Acute otitis media is the most common respiratory tract infection in infancy and early childhood that is managed with antimicrobial agents. Ninety-three per cent of the cases diagnosed in Spain are treated with antibiotics, and \textit{Streptococcus pneumoniae} and untypeable \textit{Haemophilus influenzae} are the most frequently isolated pathogens. The aim of this work was to evaluate the usefulness of amoxicillin, amoxicillin/clavulanate and ceftriaxone for the empirical treatment of acute otitis media, looking at the pharmacokinetic variability and the antimicrobial susceptibility of paediatric strains of the two main pathogens responsible for AOM in Spain, \textit{Streptococcus pneumoniae} and \textit{Haemophilus influenzae}.

\textbf{Methods: }Free-drug plasma concentrations were simulated and the probability of target attainment at each minimum inhibitory concentration and the cumulative fraction of response (CFR) were determined. Microbiological susceptibility information was extracted from SAUCE 3 surveillance.

\textbf{Results: }CFR with amoxicillin varied from 83\% to 96\% against \textit{S. pneumoniae} and from 78\% to 86\% against \textit{H. influenzae}. CFR was always >85\% with amoxicillin/clavulanate. With the 3-day ceftriaxone regimen, the probability of achieving free concentrations above MIC at 72 hours significantly increased compared to the single dose, with which CFR ranged from 70\% to 84\%.

\textbf{Conclusions: }High-dose amoxicillin (at least 80 mg/kg/day) should be the first-line therapy in uncomplicated infections, whereas amoxicillin/clavulanate (40 mg/kg/day) should be the choice when additional coverage for \textit{H. influenzae} is desired. Administration of 3 daily doses of ceftriaxone increases bacteriological eradication probability when compared with one-day regimen, although additional clinical evaluations are necessary to establish the best target attainment with ceftriaxone.

\section*{Evaluacion farmacocinetica/farmacodinamica de agentes antimicrobianos para el tratamiento de la otitis media aguda en España}

\textbf{Resumen}

\textbf{Introducción: }La otitis media aguda (OMA) es la infección del tracto respiratorio más común en la infancia que es tratada con agentes antimicrobianos. El noventa y tres por ciento de los casos diagnosticados en España se tratan con antibióticos, siendo \textit{Streptococcus pneumoniae} y \textit{Haemophilus influenzae} no tipable los patógenos aislados más frecuentes. El objetivo de este trabajo ha sido evaluar la utilidad de amoxicilina, amoxicilina/clavulánico y ceftriaxona en el tratamiento empírico de OMA teniendo en cuenta la variabilidad farmacocinética y la sensibilidad antimicrobiana de las cepas pediátricas de los dos patógenos principales responsables de OMA en España, \textit{Streptococcus pneumoniae} y \textit{Haemophilus influenzae}.

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Methods: Se simularon las concentraciones de fármaco libre para cada antibiótico y se calculó la probabilidad de alcanzar el objetivo terapéutico para cada valor de concentración mínima inhibidora (CMI) y la fracción de respuesta acumulada (CFR).

Results: La CFR de amoxicilina osciló entre el 83% y el 96% frente a S. pneumoniae y entre el 78% y el 86% para H. influenzae. En el caso de amoxicilina/clavulánico, la CFR fue siempre >85%. Con ceftriaxona durante 3 días, la probabilidad de alcanzar concentraciones libres por encima de la CMI a las 72 horas fue significativamente superior a la probabilidad obtenida con una sola dosis, con valores de CFR que oscilaron entre el 70% y el 84%.

Conclusions: Amoxicilina a altas dosis debería ser la primera opción para el tratamiento de infecciones no complicadas, mientras que amoxicilina/clavulánico deberá utilizarse cuando se sospeche que H. influenzae puede ser responsable de la infección. La administración de ceftriaxona durante 3 días incrementa la probabilidad de erradicar la infección respecto a la administración de una única dosis, aunque son necesarios estudios clínicos para establecer el mejor objetivo terapéutico con ceftriaxona.
The time that free drug concentrations were maintained above the MIC \( (f_{T>MIC}) \) was determined using the Splus software (Insightful, Seattle, WA). The provability of target attainment (PTA) was calculated by counting the subjects who achieved \( f_{T>MIC} \) for at least 50% of the dosing interval. The cumulative fraction of response (CFR) for each dose administration regimen was calculated by multiplying the PTA at each MIC by the fraction of organism susceptible at that concentration of the respective MIC distribution. The sum of those individual products is the CFR\(^{10}\), and can be interpreted as the probability of successful treatment of infections caused by bacteria with a specific susceptibility pattern in the population studied.

In the case of ceftriaxone, in determining the amount that free plasma concentrations need to exceed MICs to achieve bacteriological eradication, the frequency of times above the MIC for 24, 48, 72, 96, and 120 hours was evaluated. CFR was calculated as the probability to achieve \( f_{T>MIC} \) considering the MIC distribution.

**Results**

Figures 1 and 2 show the antimicrobial susceptibility of *S. pneumoniae* and *H. influenzae* paediatric strains to amoxicillin and amoxicillin/clavulanate, respectively. According to breakpoints...
recommended by CLSI for non-meningeal infections\textsuperscript{11}, both were very active against \textit{S. pneumoniae} with susceptibilities \textgreater90\%. Amoxicillin/clavulanate was also very active against \textit{H. influenzae}, with a susceptibility of 100\%, but amoxicillin was less active. Among \textit{H. influenzae} isolates, 15.5\% were \textbeta-lactamase positive-ampicillin resistant strains and 2.7\% were \textbeta-lactamase negative ampicillin resistant strains, presenting diminished susceptibility to ampicillin with MIC\textless2 mg/L.

The results of the analysis of the PTA by MIC for both antibiotics are also shown in Figures 1 and 2. The achieved PTA with high doses (\textgeq80 mg/kg/day) was \textgreater80\% up to an MIC of 2 mg/L. The PTA with the lowest doses was also higher than 80\% up to an MIC of 1 mg/L.

Table 1 shows the assessment of CFR for amoxicillin and amoxicillin/clavulanate. When amoxicillin was evaluated, CFR varied from 83\% to 96\% against \textit{S. pneumoniae}, and from 78\% to 86\% against \textit{H. influenzae}. For amoxicillin/clavulanate, CFR was always \textgreater85\%.

Figure 3 shows the antimicrobial susceptibility for ceftriaxone. This antibiotic was very active against \textit{S. pneumoniae} and \textit{H. influenzae}, with susceptibilities of 96\% and 100\%, respectively. Figure 4 shows ceftriaxone target attainment to maintain free drug concentration above MIC at 24, 48, 72, 96 and 120 hours for all posologies. When a single dose of 50 mg/kg im ceftriaxone was simulated, the proportion of virtual patients with free plasma concentrations that exceeded the MICs of 0.015, 0.03, 0.06, 0.125 and 0.25 mg/L at 24 hours was 85\%, 83\%, 80\%, 77\% and 73\%, respectively. These values decreased further as time after dosing increased (at 48, 72, 96 and 120 hours post-dose). Slightly more favourable results were achieved with the highest dose (100 mg/kg iv or im). Considering the antimicrobial susceptibility of \textit{H. influenzae} to ceftriaxone (99.8\% isolates presented MICs \textless0.25 mg/L), all dose regimens provided \textit{fT}_{\text{MIC}} longer than 24 hours in more than 70\% of the patients. However, a significant number of strains had MICs of 1 mg/L (16.6\%) or 2 mg/L (3.5\%) against \textit{S. pneumoniae}. In these cases, target attainment at 24 hours decreased significantly (50\% for 50 mg/kg and 66\% for 100 mg/kg). Consecutively, CFR values were higher for \textit{H. influenzae} than for \textit{S. pneumoniae} (Table 2). When the 3-day regimen is considered, the probability to achieve \textit{fT}_{\text{MIC}} for 72, 96 and 120 hours significantly increased compared to the single dose.

**Discussion**

Considering that AOM is typically treated empirically, the treatment of choice should target the most frequently isolated pathogens. In this study PK/PD simulations were performed to evaluate different dose regimens of amoxicillin, amoxicillin/clavulanate and ceftriaxone, taking into account the antimicrobial susceptibility of paediatric strains of the two main pathogens responsible for the disorder in Spain, \textit{S. pneumoniae} and \textit{H. influenzae}, together with the pharmacokinetic variability in paediatric population.

When PK/PD principles are employed, PK and PD profiles of antimicrobials at infection site should be taken into account. However, we have used unbound plasma drug concentrations to

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**Table 1**

<table>
<thead>
<tr>
<th>MIC (mg/L)</th>
<th>S. pneumoniae</th>
<th>H. influenzae</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.015</td>
<td>27.5</td>
<td>55.4</td>
</tr>
<tr>
<td>0.03</td>
<td>12.6</td>
<td>22.8</td>
</tr>
<tr>
<td>0.06</td>
<td>7.8</td>
<td>20.5</td>
</tr>
<tr>
<td>0.125</td>
<td>2.1</td>
<td>2.7</td>
</tr>
<tr>
<td>0.25</td>
<td>0.3</td>
<td>0.2</td>
</tr>
<tr>
<td>0.5</td>
<td>0.2</td>
<td>0.3</td>
</tr>
<tr>
<td>1</td>
<td>0.3</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Table showing expected cumulative fractions of response (CFR) for amoxicillin and amoxicillin/clavulanate. The target chosen was 50\% of unbound concentration above the MIC. For amoxicillin/clavulanate, only amoxicillin doses are indicated.

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**Figure 3.** MIC distribution of ceftriaxone against 373 paediatric strains of \textit{S. pneumoniae} (white bars) and 438 paediatric strains of \textit{H. influenzae} (grey bars).
Moreover, when the parameter that predicts, recommend high-
76 54 41 32 26 83 64 51 42 35
70 49 36 28 23 81 62 49 40 33
77 56 42 33 27 84 66 52 43 36
and Israel
71 48 35 27 21 82 61 48 38 31
was lower
4
To achieve a CFR
16x773
Table 2
Expected cumulative fractions of response (CFR) for ceftriaxone. The target chosen
was 80 mg/kg/day, although with all posologies target expectation
for what is happening at the site of infection. If a robust relationship
can be found between bacterial inhibition and killing and plasma
PK/PD, the model may be considered validated
16
. In the treatment of infectious diseases one may accept a risk of
treatment failure in 10% to 20% of children for infections that are
not life-threatening and have low morbidity
17
. To achieve a CFR
≥90% against S. pneumoniae, high-dose amoxicillin was needed, at
least 80 mg/kg/day, although with all posologies target expectation
was higher than 80%. However, when H. influenzae is the pathogen
involved, high-dose amoxicillin had an 82–86% likelihood of achiev-
ing the target pharmacodynamic exposure, but CFR >90% was never
achieved. When considering amoxicillin/clavulanate, a CFR <90%
was only obtained when 20 mg/kg q12 h was simulated.

Current AOM management guidelines recommend high-dose
amoxicillin as the first-line drug of choice in children
18
. However, the probability of a successful outcome of high-dose amoxi-
cillin against H. influenzae calculated using the Global Respiratory
Antimicrobial Surveillance Project (GRASP) database
19
was lower
than 65%. This value, lower than those obtained in our study, could
be explained by the regional susceptibility patterns. Amoxicillin
susceptibility against S. pneumoniae and H. influenzae was doc-
umented in 80.6% and 54.5% of isolates from the GRASP study,
whereas in SAUCE 3 it was 90.1% and 81.7%, respectively. These
discrepancies justify different recommendations for empirical
antibiotic treatment. Considering our results, high-dose amoxi-
cillin should be confirmed as the first-line choice for children
with AOM in Spain (CFR >80%). In patients who have severe ill-
ness, and in those for whom additional coverage for H. influenzae
is desired, selected therapy should be amoxicillin/clavulanate.
Studies carried out in the US
19
and Israel
4, recommend high-
dose amoxicillin/clavulanate (90 mg/kg/day), but 13 mg/kg q8 h
provides a high probability of achieving the requisite pharmaco-
dynamic exposure in Spain (CFR >90%).

The strains not covered by either amoxicillin or amoxi-
cillin/clavulanate would be responsible for the failure of the
treatment with these agents. Dagan
4 observed that apart from
amoxicillin/clavulanate, ceftriaxone was the only agent that
successfully prevented bacterial persistence for the pathogens
involved in AOM. For this drug, the target of continuously achieving
36 hours of free concentrations in tonsil tissue that exceeded

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>S. pneumoniae</th>
<th>H. influenzae</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mg/kg iv</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sd</td>
<td>70</td>
<td>24</td>
</tr>
<tr>
<td>3 daily doses</td>
<td>73</td>
<td>48</td>
</tr>
<tr>
<td>100 mg/kg iv</td>
<td>76</td>
<td>72</td>
</tr>
<tr>
<td>sd</td>
<td>70</td>
<td>76</td>
</tr>
<tr>
<td>3 daily doses</td>
<td>77</td>
<td>54</td>
</tr>
<tr>
<td>50 mg/kg im</td>
<td>71</td>
<td>50</td>
</tr>
<tr>
<td>sd</td>
<td>71</td>
<td>50</td>
</tr>
<tr>
<td>3 daily doses</td>
<td>74</td>
<td>51</td>
</tr>
<tr>
<td>100 mg/kg im</td>
<td>77</td>
<td>32</td>
</tr>
<tr>
<td>sd</td>
<td>77</td>
<td>57</td>
</tr>
<tr>
<td>3 daily doses</td>
<td>78</td>
<td>57</td>
</tr>
</tbody>
</table>
* sd: single dose.
the MIC has been considered as the criterion for defining microbiological success in the treatment of tonsillopharyngitis. A target for treatment of AOM has not been established: this is why we calculated the probability to achieve plasma free drug concentrations above the MIC at 24, 48, 72, 96 and 120 h.

Leibovitz et al. showed a 48% bacteriological failure rate with a single 50 mg/kg ceftriaxone dose against penicillin-susceptible S. pneumoniae. Our results do not reflect such a high probability of treatment failure, as a susceptibility of 96% was documented in SAUCE 3, whereas 17-20% of strains isolated in the Leibovitz study were non-susceptible to ceftriaxone.

Estimated CFRs of ceftriaxone for H. influenzae are lower than expected, if we consider that 100% of the Spanish strains are susceptible (MICs ≤ 1 mg/L). This could be due to the fact that the target we chose may not be the most suitable one. The time above the MIC during the 24-h dosing interval for MEF is much greater than the $T_{\text{MIC}}$ in serum. Therefore, a more favourable scenario could be expected if we consider MEF concentrations instead of unbound plasma concentrations. Hence, the search for an adequate target for ceftriaxone in AOM is necessary, as Blumer established for tonsillopharyngitis and availability of clinical data on microbiological success rate is very important in order to contrast these results.

Recently studies have documented that a 3-day ceftriaxone regimen is significantly superior to a 1-day one in the treatment of non-responsive AOM caused by penicillin-resistant S. pneumoniae. We showed that CFR is still higher than 70% for S. pneumoniae 72 h after starting a 3-day treatment, while it decreased significantly after 24 h with a single dose. However, pharmacodynamic exposure target for both one-day and three-day dose regimens should be better established and confirmed with clinical data.

In spite of the results reported above, the following issues should be considered. Firstly, paediatric pharmacokinetic data of antibiotics are scarce and are obtained from a non-homogeneous population in relation to age. This leads to large interindividual variability, which was included in our pharmacokinetic model. Secondly, we used microbiological data from paediatric isolates, but not all of them were recovered from patients with otitis media. The reason for including strains from MEF and from the lower respiratory tract is that the microorganisms from MEF are more resistant, since in Spain, samples from MEF are only collected from the more severe cases or recurrence of AOM. The selection of these strains will provide biased information on the success of empirical treatments. The use of strains from the lower respiratory tract will provide more realistic information of susceptibility of strains causing AOM. Thirdly, this study did not consider the changing microbiology of AOM after widespread use of heptavalent pneumococcal vaccine (PCV7), which has been described in different countries. PCV7 has not been included into the vaccination schedule in Spain. If this occurred, the coverage could be similar as for any other vaccine included in the vaccination schedule (95%). In that case, this could result in a shift in frequency of causative bacterial pathogens responsible for AOM, and the results observed with this simulation exercise would have to be recalculated. Finally, this study has been developed using susceptibility data representative of bacteria causing non-complicated AOM in Spain. Consequently, caution should be taken before applying these findings to complicated/refractory infections or to other countries with different pathogen distribution data or different susceptibility patterns. Moreover, susceptibility data are based on a collection of isolates from the SAUCE 3 project, obtained during 2000-2001 and they may have changed since then. In the event of significant modifications in susceptibilities from new available data, new PK/PD evaluations should be performed in order to detect changes in the efficacy profiles of the antimicrobials.

In conclusion, considering the current susceptibility of bacterial pathogens most frequently isolated in AOM in Spain, high-dose amoxicillin should be the first-choice for children with uncomplicated or non-refractory infection. Amoxicillin/clavulanate will provide the highest CFR (>90%) against both S. pneumoniae and H. influenzae. Differences with other studies may be explained by variations in antibiotic susceptibility patterns between countries. Results obtained with one-day ceftriaxone regimen indicate that it would be insufficient to achieve an acceptable bacteriological success rate if S. pneumoniae is responsible for the infection. Administration of 3 daily consecutive doses increases bacteriological eradication. Additional clinical evaluations will be necessary to establish the best target attainment for the treatment of AOM with ceftriaxone.

Conflict of interest

The authors have no conflicts of interest to declare.

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References