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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Abstract

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 *Streptococcus pneumoniae* and *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, *Streptococcus pneumoniae* and *Haemophilus influenzae*.

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.

Results: CFR with amoxicillin varied from 83% to 96% against *S. pneumoniae* and from 78% to 86% against *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%.

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 *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.

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Evaluacion farmacocinetica/farmacodinamica de agentes antimicrobianos para el tratamiento de la otitis media aguda en España

Resumen: 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 *Streptococcus pneumoniae* y *Haemophilus influenzae* no tipable los patógenos aislados más frecuentes. El objetivo de este trabajo ha sido evaluar la utilidad de amoxicilina, amoxicilina/clavulanico 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, *Streptococcus pneumoniae* y *Haemophilus influenzae*.

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Introduction

Acute otitis media (AOM) 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 as AOM in Spain are treated with antibiotics, and Streptococcus pneumoniae and untypeable Haemophilus influenzae are the most frequently isolated pathogens.

It is well known that antibiotics shorten the course of AOM, but many cases remit spontaneously without complications. Thus clinicians should avoid prescribing antibiotics routinely. Initial observation seems to be suitable for many children, if follow-up can be assured, whereas antibiotic treatment may be necessary in the very young (spontaneous resolution is lower in children younger than 2 years) or in severe or prolonged cases. When antibiotic therapy is indicated, selection of the most appropriate antibiotic should be based on the patient’s risk factors, physical examination, symptoms, local resistance patterns and treatment guidelines. By using pharmacokinetic (PK) and pharmacodynamic (PD) principles, an evaluation of the usefulness of treatments with antibiotics can be made in order to predict the likelihood of a successful clinical outcome.

In patients treated with β-lactams, bacterioidal eradication can be predicted if free drug concentrations at the site of infection are above the minimum inhibitory concentrations (MIC) of the pathogen for a time interval that exceeds 40%-50% of the dosing interval.

In a recent study, we evaluated the antimicrobial treatments in children with AOM in Spain taking into account the PK/PD approach. Only ceftriaxone and high-dose amoxicillin/clavulanate provided adequate efficacy indexes against S. pneumoniae and H. influenzae. Macrolides and azithromycin were not included in the study as they should not be empirically used in Spain due to the resistance of S. pneumoniae.

In that study, neither PK nor PD variability were considered. But, in fact, all organisms display a range of susceptibilities to any given antibiotic. Besides, a distribution of serum antibiotic concentrations is observed in any population receiving the same antibiotic. Thus, the main objective of this work was to evaluate the usefulness of amoxicillin, amoxicillin/clavulanate and ceftriaxone for the treatment of AOM in Spain, assessing the probability of achieving the requisite PD exposure against S. pneumoniae and H. influenzae and taking into account the PK and PD variability in a simulated paediatric population.

Methods

Acquisition of microbiological data

Information on the minimum inhibitory concentration (MIC) values of amoxicillin, amoxicillin/clavulanate and ceftriaxone from 373 paediatric strains of S. pneumoniae and 438 of H. influenzae was extracted from the SAUCE 3 surveillance and provided by the Medical Department of GlaxoSmithKline. The clinical isolates of S. pneumoniae and H. influenzae were obtained from community-acquired respiratory tract infections and collected between November 2001 and October 2002. About 49% of the S. pneumoniae and 32% of the H. influenzae isolates were from middle ear samples, whereas 32% and 67%, respectively, were collected from lower respiratory tract and 18% and 1.5% respectively, from blood. A complete description of study is provided in Reference 6.

Monte Carlo simulation

The following drug regimens were evaluated: amoxicillin and amoxicillin/clavulanate 20 mg/kg, 40 mg/kg, 45 mg/kg and 50 mg/kg every 12 h; 13 mg/kg, 27 mg/kg, 30 mg/kg and 33 mg/kg every 8 h; ceftriaxone 50 mg/kg and 100 mg/kg intramuscularly and intravenously, single dose and a 3-day regimen. A 5000 subject Monte Carlo simulation was employed to recreate steady-state free drug plasma concentration-time profiles on the basis of models and model parameter estimates reported previously in paediatrics.

Amoxicillin profiles were generated using the information provided by Canafax et al., assuming a one-compartment model. The mean population values for apparent volume of distribution (V/F), first order elimination rate constant (K) and first order absorption rate constant (K) were 1.44 L/kg, 0.276 h⁻¹ and 1.77 h⁻¹, respectively. The value of the unbound fraction (fu) in plasma was 0.8. The values for interindividual variability (IIV) (expressed as coefficient of variation) were 26%, 50% and 56%, respectively.

Ceftriaxone plasma concentration-time profiles were created based on a recent pharmacokinetic evaluation. A three-compartment model was used with the following pharmacokinetic parameter values (IIV expressed as coefficient of variation in parenthesis): V/F (L): 2.13 (84); apparent total plasma clearance (CL/F (L/h)): 0.556 (27); K23 (h⁻¹): 3.12 (78); K32 (h⁻¹): 5.78 (37); K24 (h⁻¹): 4.73 (69); K42 (h⁻¹): 6.13 (61), where the K’s correspond to the first order rate distribution constant between the central and peripheral compartments, or absorption. When intramuscular administration was considered, bioavailability (F) and K (h⁻¹) of 1 and 3.09 (183), were used.

All simulations were performed with NONMEM (Version V, Level 1.1, GloboMax LLC, Hanover, MD). Individual pharmacokinetic parameters were assumed to follow a log-normal distribution with absence of covariance. The values used for fu and F during the simulation exercise were the typical population estimates. Unbound plasma concentrations were simulated without residual error.

For amoxicillin and amoxicillin/clavulanate, pharmacodynamic exposures for simulated dose regimens were assessed as follows.
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, 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 ceftaxone, 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...
Table 1

<table>
<thead>
<tr>
<th>CFR (%)</th>
<th>S. pneumoniae</th>
<th>H. influenzae</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 mg/kg q12h</td>
<td>83</td>
<td>78</td>
</tr>
<tr>
<td>40 mg/kg q12h</td>
<td>91</td>
<td>82</td>
</tr>
<tr>
<td>45 mg/kg q12h</td>
<td>92</td>
<td>83</td>
</tr>
<tr>
<td>50 mg/kg q12h</td>
<td>93</td>
<td>83</td>
</tr>
<tr>
<td>13 mg/kg q8h</td>
<td>89</td>
<td>82</td>
</tr>
<tr>
<td>27 mg/kg q8h</td>
<td>95</td>
<td>85</td>
</tr>
<tr>
<td>30 mg/kg q8h</td>
<td>96</td>
<td>85</td>
</tr>
<tr>
<td>33 mg/kg q8h</td>
<td>96</td>
<td>86</td>
</tr>
<tr>
<td>Amoxicillin/clavulanate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 mg/kg q12h</td>
<td>89</td>
<td>85</td>
</tr>
<tr>
<td>40 mg/kg q12h</td>
<td>94</td>
<td>93</td>
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<tr>
<td>45 mg/kg q12h</td>
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<tr>
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<td>95</td>
</tr>
<tr>
<td>13 mg/kg q8h</td>
<td>93</td>
<td>93</td>
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<tr>
<td>27 mg/kg q8h</td>
<td>97</td>
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<tr>
<td>30 mg/kg q8h</td>
<td>97</td>
<td>98</td>
</tr>
<tr>
<td>33 mg/kg q8h</td>
<td>97</td>
<td>99</td>
</tr>
</tbody>
</table>

q12 h, every 12 h; q8 h, every 8 h.

recommended by CLSI for non-meningeal infections\(^\text{11}\), both were very active against *S. pneumoniae* with susceptibilities >90%. Amoxicillin/clavulanate was also very active against *H. influenzae*, with a susceptibility of 100%, but amoxicillin was less active. Among *H. influenzae* isolates, 15.5% were β-lactamase positive-ampicillin resistant strains and 2.7% were β-lactamase negative ampicillin resistant strains, presenting diminished susceptibility to ampicillin with MIC \(\geq 2\) 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 (\(\geq 80\) mg/kg/day) was >80% 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 *S. pneumoniae*, and from 78% to 86% against *H. influenzae*. For amoxicillin/clavulanate, CFR was always >85%.

Figure 3 shows the antimicrobial susceptibility for ceftriaxone. This antibiotic was very active against *S. pneumoniae* and *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 *H. influenzae* to ceftriaxone (99.8% isolates presented MICs \(\leq 0.25\) mg/L), all dose regimens provided \(\text{fT} > \text{MIC}\) 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 *S. pneumoniae*. In these cases, target attainment at 24 hours decreased significantly (50% for 50 mg/kg and 60% for 100 mg/kg). Consecutively, CFR values were higher for *H. influenzae* than for *S. pneumoniae* (Table 2). When the 3-day regimen is considered, the probability to achieve \(\text{fT} > \text{MIC}\) 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, *S. pneumoniae* and *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
Figure 4. Ceftriaxone target attainment for maintaining free drug concentrations above MIC. The figure shows the ceftriaxone time above MIC in plasma with target attainment at 24 h (filled diamond), 48 h (open square), 72 h (filled triangle), 96 h (cross) and 120 h (open circle).

perform simulations because they can accurately predict middle ear fluid (MEF) concentrations, as has been explained previously in the literature. Moreover, when the parameter that predicts efficacy is determined, it is by using the plasma levels as a surrogate 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.

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. 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 achieving 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. However, the probability of a successful outcome of high-dose amoxicillin against H. influenzae calculated using the Global Respiratory Antimicrobial Surveillance Project (GRASP) database 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 documented 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 amoxicillin should be confirmed as the first-line choice for children in Spain (CFR > 80%). In patients who have severe illness, and in those for whom additional coverage for H. influenzae is desired, selected therapy should be amoxicillin/clavulanate. Studies carried out in the US and Israel recommend high-dose amoxicillin/clavulanate (90 mg/kg/day), but 13 mg/kg q8 h provides a high probability of achieving the requisite pharmacodynamic exposure in Spain (CFR > 90%).

The strains not covered by either amoxicillin or amoxicillin/clavulanate would be responsible for the failure of the treatment with these agents. Dagan 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 2

<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 49 36 28 23</td>
<td>81 62 49 40 33</td>
</tr>
<tr>
<td>3 daily doses</td>
<td>73 52 40</td>
<td>82 63 50</td>
</tr>
<tr>
<td>100 mg/kg iv</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sd</td>
<td>76 54 41 32 26</td>
<td>83 64 51 42 35</td>
</tr>
<tr>
<td>3 daily doses</td>
<td>77 57 45</td>
<td>84 66 53</td>
</tr>
<tr>
<td>50 mg/kg im</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sd</td>
<td>71 48 35 27 21</td>
<td>82 61 48 38 31</td>
</tr>
<tr>
<td>3 daily doses</td>
<td>74 52 40</td>
<td>82 63 49</td>
</tr>
<tr>
<td>100 mg/kg im</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sd</td>
<td>77 56 42 33 27</td>
<td>84 66 52 43 36</td>
</tr>
<tr>
<td>3 daily doses</td>
<td>78 57 45</td>
<td>85 66 53</td>
</tr>
</tbody>
</table>

* sd: single dose.
the MIC has been considered as the criterion for defining micro-
biological success in the treatment of tonsillopharyngitis. A target
for treatment of AOM has not been established; this is why we cal-
culated 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 sus-
ceptible (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 micro-
biological success rate is very important in order to contrast these
results.
Recently studied 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
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. Sec-
ondly, 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 respira-
tory 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 heptava-
 lent pneumococcal vaccine (PCV7), which has been described in
different countries. PCV7 has not been included in the vac-
cination 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 fre-
cuency 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 per-
formed in order to detect changes in the efficacy profiles of the
antimicrobials.
In conclusion, considering the current susceptibility of bacte-
rial pathogens most frequently isolated in AOM in Spain, high-dose
amoxicillin should be the first-line choice for children with uncom-
plicated 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 coun-
tries. Results obtained with one-day ceftriaxone regimen indicate
that it would be insufficient to achieve an acceptable bacteriologi-
cal success rate if S. pneumoniae is responsible for the infection.
Administration of 3 daily consecutive doses increases bacteriologi-
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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