Escherichia coli. These in vitro data indicate that RD-3 may show considerable promise for both genital and respiratory infections with mycoplasmas, but its clinical utility will depend upon its toxicity and pharmacokinetics.

Acknowledgements

We thank Professor Ragavachari Raghunathan, Department of Organic Chemistry, University of Madras, for providing the compound RD-3.

Funding

This study was funded in part by financial support from the University of Madras, Chennai, India.

Transparency declarations

None to declare.

References


Journal of Antimicrobial Chemotherapy
doi:10.1093/jac/dkp376
Advance Access publication 14 October 2009

Susceptibility of pneumococci causing meningitis in Spain and prevalence among such isolates of serotypes contained in the 7-valent pneumococcal conjugate vaccine

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Keywords: laboratory-based surveillance, cerebrospinal fluid, Streptococcus pneumoniae

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Sir,

Streptococcus pneumoniae remains the most common cause of bacterial meningitis in children in the USA, although since the introduction of the 7-valent pneumococcal conjugate vaccine (PCV-7) rates have decreased despite the increase in meningitis caused by non-PCV-7 serotypes. In Spain the decrease in the prevalence of PCV-7 serotypes among the global population of invasive pneumococci after the introduction of PCV-7 was not as marked as in the USA, probably due to irregular and lower coverage. After vaccine introduction in 2001, distribution was via the private market because of the selective introduction into childhood vaccination calendars (it was only introduced in the Madrid region from November 2006). A recently published ecological analysis of invasive isolates over time in Spain suggested that PCV-7 vaccination in children had produced a herd effect (with respect to prevalence of PCV-7 isolates and antibiotic susceptibility) in adults. It has also been reported that the incidence of pneumococcal meningitis among children <5 years old significantly decreased in Spain from 2001 to 2006, without evidence of changes in the incidence of meningitis caused by non-vaccine serotypes. Although a small proportion of invasive pneumococcal infections present as meningitis, it has a high case-fatality rate. Whether the empirical use of cefotaxime for meningitis needs to be continued in countries with increasing PCV-7 uptake needs to be monitored. We considered isolates from CSF received in the Spanish Reference Laboratory for Pneumococci (SRLP) in the current decade to analyse their susceptibility and prevalence of PCV-7 serotypes.

All CSF isolates of S. pneumoniae sent voluntarily from all over the country to the SRLP (passive, laboratory-based surveillance system) from January 2000 to December 2008 were analysed. Isolates were serotyped by Quellung reaction and/or dot blot assay, and susceptibility was determined by agar dilution. Current CLSI meningitis susceptibility breakpoints for penicillin (MIC≤0.06 mg/L) and cefotaxime (MIC≤0.5 mg/L), and susceptibility breakpoints of MIC≤1 mg/L for vancomycin and MIC≤2 mg/L for levofloxacin were used. Trends over time were explored by linear regression analysis. P≤0.05 was considered significant.

Data are shown in Table 1. Of the 1397 CSF isolates received between January 2000 and December 2008, 923 (66.1%) were from adults and 474 (33.9%) from children ≤14 years of age. No significant trends in the percentage of CSF isolates among invasive isolates were found in the three populations: total population (R²=0.008, P=0.823), adults (R²=0.240, P=0.180) and children (R²=0.395, P=0.070), although in children there was a continuous decrease from 15.5% in 2003 to 9.8% in 2008.

The prevalence of PCV-7 serotypes among CSF isolates showed significant decreasing linear trends in the total population (R²=0.914, β=-0.956, P<0.001), adults (R²=0.819, β=-0.905, P<0.001) and children (R²=0.870, β=-0.933, P<0.001), with a significantly higher decreasing slope in children than in adults (B coefficient=-6.307, 95% CI=-8.485 to -4.128 in children versus B coefficient=-3.495, 95% CI=-4.963 to -2.027 in adults).

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Penicillin susceptibility showed a significant increasing linear trend in the study period when analysing the total population ($R^2=0.741$, $\beta=0.861$, $P=0.003$) and children (although with lower correlation: $R^2=0.584$, $\beta=0.764$, $P=0.017$), but not in adults ($R^2=0.150$, $P=0.303$). In the period 2001–08 susceptibility rates were 80% to cefotaxime and 100% to vancomycin and levofloxacin. 

In the 2000s there was an increase in the number of invasive isolates sent voluntarily to the SRLP (Table 1), probably reflecting greater awareness of and interest in invasive pneumococcal disease by paediatricians, and on the effect of PCV-7 introduction on susceptibility and serotype ecology among the medical community.3,4 PCV-7 was introduced in Spain in 2001 with distribution (doses/1000 inhabitants النساء C20 59 months age/year) increasing from 193.34 in 2002 through 392.64 in 2005 and 411.90 in 2007 up to 500 in 2008.3 Data in this study indicate that PCV-7 vaccination in children had a herd effect in adults since the prevalence of PCV-7 serotype isolates among CSF isolates significantly decreased not only in children but also in adults. However, this herd effect was not demonstrated when analysing penicillin susceptibility in CSF isolates, because the significant linear increase in penicillin susceptibility in the total population and in children could not be shown in adults, in contrast to previous studies analysing all invasive isolates where penicillin susceptibility increased in both populations.3 Nevertheless the non-susceptibility rates to penicillin (and to a lesser extent to cefotaxime), using meningitis breakpoints, indicate the need to maintain cefotaxime or ceftriaxone plus vancomycin as empirical treatment in suspected pneumococcal meningitis in Spain.

**Funding**

This study was carried out as part of our routine work. O. R. received funding from the Spanish Network for Research in Infectious Diseases (REIPI RD06/0008).

**Transparency declarations**

None to declare.

**References**

Use of therapeutic drug monitoring in the long-term valaciclovir therapy of relapsing herpes simplex virus encephalitis in children

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Keywords: aciclovir, paediatric, brain, central nervous system penetration

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Sir,

Adequate therapy of herpes simplex virus (HSV) encephalitis relies upon good central nervous system (CNS) delivery of aciclovir and adequate duration of treatment as shorter courses of treatment have been associated with relapse of disease. The current paediatric practise is to treat with 3 weeks of intravenous (iv) aciclovir at 1500 mg/m²/day. Despite this, relapses have been reported that may represent either frank viral relapse or a post-infectious movement disorder. Long-term oral aciclovir therapy like that used in neonatal HSV-2 disease may benefit children with HSV-1 encephalitis. Valaciclovir is rapidly metabolized to aciclovir producing plasma concentrations three to five times higher than oral aciclovir and may thus provide a better alternative to oral aciclovir. Its use in children in a variety of herpes virus infections has been reviewed, but is confined mainly to non-CNS disease.

Here, we report our experience in the therapeutic monitoring of plasma and cerebral spinal fluid (CSF) aciclovir concentrations in five children. Three very young children aged 20 months (patient 1), 11 months (patient 2) and 6 months (patient 3) with relapsing HSV-1 encephalitis were treated with long-term oral valaciclovir after completing a course of iv aciclovir at relapse. Two children (patients 4 and 5) with suspected viral encephalitis were treated with iv aciclovir. CSF aciclovir concentrations were only measured when a lumbar puncture was clinically indicated. Parental consent was obtained for the procedures and long-term oral valaciclovir therapy.

Our therapeutic plan was to achieve a trough level that is twice the maximum published IC₅₀ of aciclovir for HSV-1 [0.022–0.22 mg/L (0.1–1 μM)] to account for the CNS penetration, which is estimated at 50%. The initial dose of oral valaciclovir was selected from published paediatric data on its use in other conditions, to achieve our theoretical trough target concentration of 0.44 mg/L. Trough aciclovir concentrations were taken prior to the administration of either oral valaciclovir or iv aciclovir. Peak aciclovir concentrations were taken 1 h after the end of a 1 h infusion of iv aciclovir or 2 h after oral valaciclovir administration according to Eksborg et al. Aciclovir concentrations were measured by a simple isocratic HPLC assay at the Bristol Centre for Antimicrobial Research and Evaluation. Intra-assay and inter-assay percentage coefficients of variation were <10% and <3.2%, respectively.

Table 1 summarizes the plasma and CSF concentrations measured in our patients. At doses of 25–40 mg/kg 8 hourly of oral valaciclovir, plasma trough concentrations of aciclovir ranged from 0.1 to 0.8 mg/L (mean 0.52, SD 0.23); whilst peak plasma aciclovir concentrations of 2.5–10.2 mg/L (mean 5.5, SD 2.4) were achieved. Our data were comparable to two other studies evaluating the pharmacokinetics of valaciclovir in children, where at doses of 10 mg/kg 8 hourly, 20 mg/kg 8 hourly and 40 mg/kg 8 hourly of oral valaciclovir, mean peak aciclovir concentrations of 2.61 mg/L, 5.17 mg/L and 7.5 mg/L, respectively, were achieved. The target trough concentration (0.44 mg/L) was achieved in all three patients on oral valaciclovir, either on initial dosage or following dose titration. The low trough level in the final measurement of patient 2 is attributable to a missed dose of valaciclovir. Trough and peak concentrations following oral valaciclovir administration of up to 40 mg/kg 8 hourly in our patients approached published values in adults (trough mean 0.72, SD 0.3; and peak mean 9.8, SD 2.6) and children (peak mean 10.3, SD 4.3) treated with 5–6 mg/kg 8 hourly (250 mg/m² 8 hourly) of iv aciclovir. Our patients treated with iv aciclovir also achieved aciclovir concentrations similar to published adult (trough mean 2.3, SD 1.4; peak mean 20.7, SD 10.2) and paediatric (peak mean 20.7, SD 5.0) data, allowing for the recognized wide inter-subject variability.

CSF aciclovir concentrations in four children (patients 2, 3, 4 and 5) on iv aciclovir and two children (patients 1 and 2) on oral valaciclovir were measured. When peak concentrations were measured, CSF penetration was 9% on two occasions in patient 2 compared with trough CSF penetrations of 80% in the same patient (Table 1). The discrepancy when measuring CNS distribution using peak concentrations is almost certainly related to the lag phase of the CSF peak. Single point measurements to reflect peak concentrations are extremely susceptible to such lag effects and are less reliable than trough values. Only multiple sampling and area under the curve (AUC) measurement can provide accurate data. Nevertheless, using CSF aciclovir trough measurements in four patients confirmed that a CSF concentration of at least 60% of plasma values could be achieved, adding more confidence to the current estimate of CSF penetration of 50%, which is the best approximation to the real value.