Daptomycin for Children in Clinical Practice Experience
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Abstract: Data on daptomycin use in the pediatric setting are scanty. We conducted a multicenter, retrospective study on 46 children treated with intravenous daptomycin at a mean dosage of 7.0 mg/kg/d, for a median of 14 days. Three children had adverse events possibly related to daptomycin. The drug was overall well tolerated, even with prolonged treatment.

Key Words: daptomycin, children, sepsis, osteomyelitis, methicillin-resistant Staphylococcus aureus

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Daptomycin (DAP) is the first-in-class cyclic lipopeptide that displays a concentration-dependent, selective bactericidal activity against Gram-positive bacteria, including methicillin-resistant Staphylococcus aureus (MRSA) and glycopeptide-resistant enterococci. As of December 2013, about 2 million adults have resistant activity against Gram-positive bacteria, including methicillin-resistant Staphylococcus aureus (MRSA) and glycopeptide-resistant enterococci. In Europe, it is approved for the treatment of complicated skin and soft tissue infections (cSSTIs), S. aureus bacteremia or right-sided endocarditis. Although children also suffer from Gram-positive infections, DAP is not labeled for patients under 18 years of age, in whom the experience on its use is scanty and the dosing regimen remains to be determined. Several pediatric clinical trials evaluating the pharmacokinetic (PK) profile, efficacy and safety of DAP are being conducted worldwide, but it will presumably take a few years before the results and the consequent prescribing information become available. Thus, at present, the available data include some anecdotal reports of outcome of DAP treatment, as well as PK and safety profiles in limited case series.

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RESULTS
A total of 46 children (25 females and 21 males) were evaluated. Their median age was 8.7 years (IQR 2.6; 14.5 years). Twenty patients (43.5%) received DAP for either a CVC-related (13) or non–CVC-related (7) sepsis; 12 (26.1%) had osteomyelitis, 11

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DAP was administered either as first-line (17 children, 37.0%) or second/third-line regimen (29 children, 63.0%); in the latter, the initial antimicrobial treatment had a median duration of 5.7 days and consisted of a glycopeptide +/− a β-lactam in 21 cases (72.4%), a β-lactam +/− an aminoglycoside or rifampin in 7 (24.1%) and linezolid in 1 case (3.5%). Two children with CVC infection also received DAP as lock therapy at 5 mg/mL during concomitant administration of IV DAP. Among patients receiving DAP as first-line empiric regimen for the suspicion of a resistant microorganism, those ultimately infected by methicillin-sensitive bacteria or penicillin-sensitive bacteria were switched to another agent after susceptibility testing results.

DAP was administered for a median of 14 days (IQR 10; 26.5 days), with 21 children (45.6%) treated for more than 14 days, and at a mean IV dose of 7.0 mg/kg/d ± 1.6 standard deviation (Table 1). Twenty-eight patients (60.9%) received DAP as monotherapy, whereas the remaining received DAP in association with a β-lactam (7), rifampin (4), an aminoglycoside (4), a fluoroquinolone (2) or metronidazole (1).

The median follow-up after DAP treatment was 76.5 days (range 14−1474 days). Three children (6.5%) had AEs possibly related to DAP: 1, under treatment for endocarditis, had rash and fever that led to DAP cessation after 4 days; the other 2, respectively, experienced a mild increase in eosinophil count and in kidney and liver functionality tests, but they completed the scheduled antimicrobial course.

No increases in CPK levels or serum creatinine were recorded. No signs or symptoms of muscular or neurological toxicity were reported.

Clinical outcomes were available for 44 patients (95.6%): a clinical cure was achieved in 25 children (56.8%), a significant improvement in 13 (29.61%) and failure in 6 (13.6%). Two children died for noninfectious reasons. All children with unsuccessful treatment received DAP as salvage therapy for a CVC-related sepsis sustained by MRSA: the treatment failure was intended as the impossibility to retain the infected indwelling long-term catheter.

Patients who improved under DAP treatment were switched to an oral drug as soon as microbiological eradication, normalization of inflammatory indexes and/or clinical stabilization were reached.

**DISCUSSION**

To our knowledge, this is the largest data series on children treated with DAP in everyday clinical practice. We found a low rate (6.5%) of AEs possibly related to DAP; in particular, the drug was suspended only in 1 patient, although almost half of the children received prolonged treatments. The most relevant AE because of DAP is muscular toxicity, requiring regular monitoring of CPK levels.1 We did not observe any CPK increase or signs/symptoms of muscular toxicity. Recently, a warning that DAP could cause life-threatening eosinophilic pneumonia has been issued5: a transient, mild eosinophilia attributed to DAP therapy was reported in 1 patient, but without pulmonary involvement. These findings are consistent with a safety analysis from the Cubicin Outcomes Registry and Experience study including 15 children treated with DAP for more than 14 days.3

The overall success rate (81.2%), considering patients cured or improved, was slightly inferior to that reported in adults. Nevertheless, given the heterogeneity of patients and of the infections treated, DAP response appears excellent, especially taking into account that the majority of children had comorbidities and/or were under immunosuppressive treatment; besides, all clinical failures occurred in children receiving DAP as salvage therapy for a CVC infected by MRSA, a condition that, according to current guidelines, requires CVC removal, as clinical failures in retained CVC can be as high as 60%.6

DAP dosage varied according to the site of infection, hospital and year of treatment: indeed, DAP dosage has been extrapolated from adult recommendations. Recent studies have documented the good tolerability and clinical superiority of higher dosages also in children.7 The latest Infectious Diseases Society of America guidelines on the management of MRSA infections suggest a DAP dosage from 6 to 10 mg/kg/d for children with bacteremia, osteomyelitis and septic arthritis.6 In ongoing clinical trials on MRSA bacteremia or osteomyelitis, DAP is used at 7 to 12 mg/kg/d, depending upon the age range.8,9

Limits of our study are intrinsically related to its retrospective and multicenter nature. Patients’ selection was obviously nonrandomized and the population enrolled was quite heterogeneous, both in terms of underlying comorbidities, type of infections and DAP dosages; also, subjects followed at a given center might have been systematically different from those at other hospitals; evaluation of AEs was not standardized and no PK data were available.

In conclusion, our study, based on a considerable number of children treated with DAP for a large array of bacterial infections, highlights that the drug was overall well tolerated even for prolonged treatments. The ongoing trials will contribute to better define the safety profile and the optimal dosage of DAP in children and to outline its regulatory indications in the pediatric setting. In this context, our study provides some useful information to clinicians for the use of DAP in children and adolescents.

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