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Daptomycin Use in Infants and Children with Gram-Positive Infections

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On September 15, 2003, the Food and Drug Administration (FDA) approved daptomycin for the treatment of complicated skin and skin structure infections in adults.[1] In 2006 an indication was added for *Staphylococcus aureus* right-sided infective endocarditis. Daptomycin provides a useful alternative to standard therapies for both methicillin-susceptible (MSSA) and methicillin-resistant (MRSA) *Staph. aureus*, and in some cases, vancomycin-resistant enterococcus (VRE). Although not yet FDA-approved for use in children, recent publications have described its benefit in treating resistant Gram-positive infections in infants and children.

Mechanism of Action

Daptomycin is a cyclic lipopeptide antibiotic derived from *Streptomyces roseosporus* with concentration-dependent bactericidal activity against aerobic Gram-positive bacteria. Daptomycin binds to calcium, forming a cationic complex that inserts into bacterial cell membranes to produce rapid depolarization. The resulting inhibition of DNA, RNA, and protein synthesis results in cell death without causing cell lysis and the release of inflammatory mediators.[1-3] Resistance to daptomycin has been reported, but is still relatively uncommon. Preexisting non-susceptibility and resistance developing during therapy have been documented in both adults and children.

Daptomycin has been shown *in vitro* and in clinical infections to have activity against *Staphylococcus aureus*, *Streptococcus agalactiae*, *Strep. dysgalactiae*, and *Strep. pyogenes*, all with a minimum inhibitory concentration (MIC) $\leq$ 1 considered susceptible, as well as vancomycin-susceptible isolates of *Enterococcus faecalis*, with a MIC $\leq$ 4 considered susceptible. Daptomycin has been shown to have *in vitro* activity against some vancomycin-resistant strains of *E. faecalis* and *E. faecium*, methicillin-resistant strains of *Staph. epidermidis* or *Staph. haemolyticus*, and *Corynebacterium jeikeium*. Clinical efficacy in these infections has not yet been established.[2]

Pharmacokinetics

Following IV administration of daptomycin, maximum plasma concentration are reached within 30 minutes (mean maximum 57.8 $\pm$ 3.0 mcg/mL with a 4 mg/kg dose and 93.9 $\pm$ 6.0 mcg/mL with a 6 mg/kg dose). Daptomycin is more than 90% protein bound, with a volume of distribution of approximately 0.1 L/kg. While effective for bacteremia and skin or soft tissue infections, it does not adequately penetrate lung epithelial lining fluid and is not recommended for the treatment of pneumonia. Nearly 80% of a daptomycin dose is eliminated in the urine as unchanged drug. A small amount is metabolized to at least three inactive compounds, but the site of metabolism is not yet known. The elimination half-life of daptomycin is 7.7-8.3 hrs in adults, with a clearance of 8.3-9.1 mL/hr/kg. Elimination half-life increases relative to renal impairment. In a pharmacokinetic study of adults with moderate renal impairment (creatinine clearance 30-50 mL/min) the average half-life was 14.70 $\pm$ 10.50 hrs, while in those with severe impairment the half-life was 27.83 $\pm$ 14.85 hrs.[2]

In response to early papers documenting the clinical efficacy of daptomycin in infants and children with Gram-positive infections, a series of pharmacokinetic studies have been performed to aid in determining an optimal dosing regimen for this patient population. In 2008, Abdel-Rahman and colleagues conducted an open-label pharmacokinetic study of 25 children (2-17 years of age) with suspected or proven Gram-positive infections.[4] All children received a 4 mg/kg dose. Systemic drug exposure was lower in the younger children, reflecting a more rapid clearance, with an area under the concentration versus time curve (AUC) of 215.3 $\pm$ 59.7 mcg•hr/mL in the children 6 years of age and younger and 374.4 $\pm$ 64.2 mcg•hr/mL in the children between 12 and 17 years of age. Volume of distribution was consistent among the groups (0.11-0.13 L/kg) and similar to that of adults. There was a trend

for shorter half-lives in the younger children, but the differences were not statistically significant (5.3 ± 1.9 hrs in the children 2-6 years of age, 5.6 ± 2.2 hrs in those 7-11 years, and 6.7 ± 2.2 hrs in those 12-17 years, p = 0.451).

Based on the more rapid clearance seen in the younger children, the authors performed a second open-label study using higher doses.[5] Twelve children between 2 and 6 years of age were stratified to receive a single 8 or 10 mg/kg dose of daptomycin over 1 hour. Mean maximum serum concentrations were 68.4 ± 9.3 mcg/mL for the 8 mg/kg dose and 79.2 ± 10.2 mcg/mL for the 10 mg/kg dose. AUC values were 371.4 ± 111.0 and 504.8 ± 139.3 mcg•hr/mL for the two doses, respectively. Values were similar in the two groups for volume of distribution (0.14 ± 0.01 and 0.14 ± 0.03 L/kg), clearance (19.5 ± 5.0 and 19.1 ± 4.5 mL/hr/kg) and half-life (5.4 ± 1.4 and 5.7 ± 0.6 hrs).

In 2012, Cohen-Wolkowiez and colleagues conducted a single-dose pharmacokinetic study in 20 infants less than 3 months of age.[6] As in the previous studies, all of the infants had suspected or proven infection and no evidence of renal dysfunction. Each patient received a 6 mg/kg dose over 1 hour. The median AUC was 262.4 mcg•hr/mL, with a volume of distribution of 0.21 L/kg, clearance of 21 mL/hr/kg, and half-life of 6.2 hrs. There were no significant relationships between gestational age, postnatal age, postmenstrual age, or serum creatinine and either the distribution or clearance of daptomycin.

Clinical Experience

Nearly a dozen case reports and retrospective studies have been published describing the use of daptomycin in infants and children. In 2007, Ardura and colleagues conducted a retrospective study of 16 children (median age 6.5 years) treated with daptomycin over a 3 year period.[3] Fifteen patients had invasive staphylococcal disease (14 with MRSA), and the remaining patient had a VRE urinary tract infection. Twelve patients had failed previous antibiotic therapy. Daptomycin was administered at a dose of 4 or 6 mg/kg once daily in all but one patient who had a creatinine clearance < 30 mL/min and was dosed every 48 hours. The median duration of treatment was 10 days (range 6-34 days). Fourteen patients (88%) demonstrated clinical improvement and were later discharged. Six of the seven patients with evaluable culture data had evidence of a bacteriologic cure.

Five case reports have described successful use of daptomycin in infants.[7-11] The doses used in these cases ranged from 4 to 15 mg/kg/day, with dosing intervals from every 12 to 48 hours. Duration of therapy ranged from 2 weeks for bacteremia to 8 weeks for a VRE endocarditis. In four of the reports, serum daptomycin concentrations were used to guide therapy. In 2008, Cohen-Wolkowiez and colleagues found that doses of 6 mg/kg every 12 hours produced concentrations similar to those seen in adults receiving 4 mg/kg once daily.[7] In their two patients, peak concentrations drawn at the end of a 1-hour infusion were 41.7 and 36.7 mcg/mL, with trough concentrations of 12.7 and 16.3 mcg/mL. A 2010 case from Sarafidis and colleagues using the same dosing regimen produced a slightly lower peak after 4 days of therapy, 27.3 mcg/mL, but a similar trough concentration of 11.6 mcg/mL.[10]

Antachopoulos and colleagues evaluated serum daptomycin levels in four children being treated for resistant Gram-positive infections.[12] The patients included three infants (26-89 days of age) and one 7-year-old. The infants were initially treated with a dose of 6 mg/kg given twice daily over 30 minutes which produced peak plasma concentrations of 10.9-17.7 mcg/mL and trough concentrations ranging from less than 4 to 8.4 mcg/mL. One of the infants developed signs of bacterial endocarditis and the daptomycin dose was increased to 15 mg/kg twice daily; cultures became negative within 5 days after the dose increase. The 7-year-old was treated with 12 mg/kg once daily, achieving a mean peak concentration of 103.4 mcg/mL and a trough of 4.2 mcg/mL. Based on their results, the authors suggest that higher doses and twice daily dosing of daptomycin may be necessary in children to achieve concentrations equivalent to that seen with standard dosing in adults.

Other pediatric daptomycin case reports include use in multi-drug resistant infections. Jaspan and colleagues described a 21-month-old treated successfully for a multidrug-resistant *E .faecium* meningitis with IV tigecycline and daptomycin (intraventricular for 7 days after the first negative culture, followed by 6 weeks of IV therapy).[13] Erturan and coworkers reported success with daptomycin in a 16-year-old with Panton-Valentine leucocidin (PVL) positive MSSA osteomyelitis.[14] In this case, a daptomycin dose of 8 mg/kg once daily was started on day 8 of hospitalization for a patient who had failed to respond to linezolid. The patient improved significantly within the next week and was discharged to home on hospital day 30.

Daptomycin treatment failure has been reported in two pediatric cases. In one of the earliest descriptions of daptomycin use in a child, Akins and colleagues treated a 13-year-old for VRE endocarditis.[15] The MIC to daptomycin at that time was 2 mcg/mL. Therapy was initiated at 6 mg/kg once daily, but increased empirically to 8 mg/kg two days later which produced a maximum concentration of 96.9 mcg/mL, with an

AUC of 593.9 mcg•hr/mL. Despite the higher dose, the patient's condition worsened and support was withdrawn 6 days later. In 2009, a 15-year-old with 90% body surface area burns was treated with daptomycin for MRSA bacteremia.[16] The patient received vancomycin initially, but developed hypotension and daptomycin was initiated at 6 mg/kg once daily. The initial MRSA isolate was susceptible with a MIC of 1 mcg/mL. On day 7, with continued positive cultures, the patient developed a fever, hypotension, and acute mental status deterioration. An echocardiogram demonstrated mitral valve vegetation and additional imaging revealed cerebral and cerebellar hemorrhagic infarcts. A cerebrospinal fluid culture grew MRSA. The isolate by this time was no longer susceptible (MIC 4 mcg/mL). Daptomycin was discontinued and vancomycin and gentamicin were initiated. Following a prolonged hospital course, the patient expired.

Warnings and Precautions

Although uncommon, daptomycin has produced severe hypersensitivity reactions, including anaphylaxis and drug rash with eosinophilia and systemic symptoms (DRESS). If signs of an allergic reaction occur, the drug should be immediately discontinued. Eosinophilic pneumonia has also been reported with daptomycin use. In a 2012 review of the literature and the FDA Adverse Event Reporting System database, Kim and colleagues identified 7 definite, 13 probable, and 38 possible cases in adults. All of these cases resolved after drug discontinuation. Symptoms consisting of fever, dyspnea, and diffuse infiltrates typically occurred 2-4 weeks after starting therapy. Treatment with corticosteroids was effective in many cases. Further use of daptomycin in these patients is contraindicated.[2,17]

Daptomycin-associated myopathy was initially reported in adults taking part in premarketing clinical trials using twice daily dosing. The clinical symptoms were often accompanied by increases in creatine phosphokinase (CPK) greater than 10 times the upper limit of normal (ULN). Some of the cases progressed to rhabdomyolysis and acute kidney failure. Subsequent studies using the currently recommended once daily dosing have demonstrated a much lower incidence of myopathy. Even with this regimen, CPK levels should be evaluated weekly. More frequent assessment should be considered for patients with underlying renal dysfunction or in those who are receiving a HMG-CoA reductase inhibitor (atorvastatin, fluvastatin, lovastatin, pitavastatin, rosuvastatin, or simvastatin). Daptomycin should be discontinued in symptomatic patients with CPK levels greater than 1,000 U/L (5 times the ULN) or in asymptomatic patients with CPK levels greater than 2,000 U/L (10 times the ULN).[2]

Adverse Effects

In daptomycin trials conducted in adults with skin or skin structure infections, the most frequently reported adverse effects were headache (in 5.4%), diarrhea (5.2%), rash (4.3%), abnormal serum transaminases (3%), elevated CPK (2.8%), urinary tract infections or hypotension (2.4%), dizziness (2.2%), and dyspnea (1%). In adults with endocarditis or bacteremia, the most frequently reported adverse effects were insomnia (9%), pharyngeal pain (8%), elevated CPK, chest pain, or edema (7%), abdominal pain, pruritus, or hypertension (6%), and sweating, or continued bacteremia/sepsis (5%). These results are similar to those seen with comparable antibiotics such as vancomycin or nafcillin.[2]

Less common, but potentially more severe adverse effects to daptomycin include the hypersensitivity reactions and myopathy previous described, as well as peripheral neuropathy, arrhythmias, tinnitus, and vision changes (all in < 1% of patients). As with other antibiotics, daptomycin may predispose patients to *Clostridium difficile*-associated diarrhea. Daptomycin can produce a falsely elevated INR and prolonged prothrombin time with some recombinant thromboplastin reagents.[2]

There is limited adverse effect information in children treated with daptomycin. The first single-dose open-label pharmacokinetic study reported no adverse effects related to the drug. In the second single-dose study of 8 and 10 mg/kg doses only two adverse effects, phlebitis and headache, were attributed to the drug; both resolved without intervention. No adverse effects were noted in the case series from Ardura and colleagues. To date, there have been no reports of CPK elevation in pediatric patients.[3-6]

Drug Interactions

As described previously, some of the cases of myopathy associated with daptomycin have been in patients also taking HMG-CoA reductase inhibitors, suggesting a possible additive or synergistic effect.[2] In a study of 20 healthy adults taking 40 mg simvastatin daily, administration of daptomycin at a dose of 4 mg/kg daily for 2 weeks produced no change in simvastatin serum concentrations and no higher rate of myopathy than in patients given a placebo. However, due to the potential risk all patients receiving the combination must be closely monitored. The manufacturer recommends that when possible the HMG-CoA reductase inhibitor be temporarily discontinued until treatment with daptomycin has been completed.

Availability and Dosage Recommendations

Daptomycin (Cubicin®; Cubist Pharmaceuticals, Inc.) is available in 500 mg single-use vials. The lyophilized powder is reconstituted prior to use with 0.9% sodium chloride to a concentration of 50 mg/mL. The dose may be administered as an IV push over 2 minutes or diluted in 0.9% sodium chloride to a final concentration of 1 mg/mL and infused over 30 minutes. Daptomycin is compatible with lactated Ringer's solution, but not with dextrose-containing solutions.[2]

The recommended dose of daptomycin in adults with skin or skin structure infections is 4 mg/kg given once daily for 7-14 days. In adults with infective endocarditis, a higher dose of 6 mg/kg should be given once daily for 3 to 6 weeks. Daptomycin should not be administered more often than once daily in adults; in clinical trials, twice daily dosing was associated with a greater incidence of myopathy. In patients with severe renal dysfunction (creatinine clearance < 30 mL/min) or in those receiving hemodialysis or chronic ambulatory peritoneal dialysis, daptomycin should be administered at the recommended dose on an every 48 hour interval.[2]

The number of pediatric patients treated with daptomycin is currently too small to allow for specific dosing guidelines. Based on the papers published to date, 4-6 mg/kg once daily may be an appropriate initial dose for children 7-17 years of age, with a dose of 6-10 mg/kg once daily for children 2-6 years of age and 6 mg/kg twice daily for infants to account for the more rapid clearance observed in this age group.

Summary

Resistant Gram-positive bacterial infections have been much less common in infants and children than in adults, but the number of cases continues to increase. There are a limited number of options for the treatment of these patients, but recent case reports suggest that daptomycin may be a valuable alternative to current therapies. Additional prospective studies are needed to clarify the role of daptomycin in the pediatric population and to determine an optimal dose.

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Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their March meeting:

1. New policies for in-line filters and the use of intravenous immune globulin were approved.
2. Recommendations from the Anticoagulation Committee regarding factor IX complex, reversal of oral anticoagulation, and use of factor VIIa were reviewed and approved.