Colistin Use in Neonates and Children With Infections Due to Carbapenem-resistant Bacteria

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Abstract: Current evidence on the use of colistin in pediatric patients for infections caused by carbapenem-resistant bacteria is based on retrospective case series. The coadministration of colistin with other antimicrobial agents was associated with a relatively low rate of nephrotoxicity and a favorable outcome in >70% of these patients. Further study of colistin pharmacokinetics in children and neonates will likely lead to optimization of dosage recommendations.

Key Words: colistin, children, neonates, carbapenem resistant, safety, efficacy, pharmacokinetics

The polymyxins are cyclic polypeptides with activity against Gram-negative bacteria; of these, polymyxin B and colistin (polymyxin E) have been developed for clinical use. Both share similar structure and spectrum of action but differ in pharmacokinetics, toxicity and other pharmacologic properties. Colistin was introduced in late 1950s but replaced in the 1970s by newer antimicrobial agents because of reported nephrotoxicity and neutropenia. Over the last years, resurgence in the clinical use of colistin has been observed worldwide, because of the emergence of difficult-to-treat infections caused by multidrug-resistant Gram-negative bacteria, including carbapenem-resistant isolates of Acinetobacter baumannii, Klebsiella pneumoniae and Pseudomonas aeruginosa. Colistin has maintained potent activity against most of these isolates, which is mediated by its strong positive charge and high affinity binding to lipopolysaccharide molecules of the outer bacterial membrane, leading to leakage of cell contents and bacterial death. Susceptibility minimal inhibitory concentration (MIC) breakpoints for A. baumannii and Enterobacteriaceae are ≤2 μg/mL (Clinical & Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST)) and for P. aeruginosa ≤2 μg/mL (CLSI) or ≤4 μg/mL (EUCAST). However, colistin has no activity against Neisseria, Proteus, Serratia, Providencia, Brucella and Burkholderia cepacia.

Although chromosomally encoded resistance to colistin has been described long ago, a mechanism of transferable resistance encoded by the mcr-1 gene located on a conjugative plasmid in Escherichia coli has recently been reported. Mcr-1 positive Enterobacteriaceae have now been isolated from animals, food of animal origin and humans all over the world. Active surveillance of colistin resistance in animal and human specimens, antimicrobial stewardship both in veterinary and human medicine and meticulous implementation of infection control practices are clearly needed in order to preserve colistin activity.

Colistin is administered parenterally as colistimethate sodium (CMS), an inactive prodrug which is hydrolyzed in vivo (and in vitro) into its active metabolite, colistin. In late 1950s, when colistin was introduced in clinical practice, most of the modern requirements for pharmacokinetic, safety and efficacy studies for adults, children and special patient groups were not in place. In addition, pharmacokinetic data generated from early studies (which led to older dosage recommendations) were based on microbiologic assays; these data are not valid, because of continuous in vitro conversion of CMS to colistin during the incubation period. Recently, analytical assays using high-performance liquid chromatography (HPLC) or liquid chromatography-tandem mass spectrometry have been developed for reliable quantification of both colistin and CMS levels. A number of well-designed pharmacokinetic studies have been performed in adults, together with studies of efficacy and safety in contemporary patient populations. Not surprisingly, pedi atric data are relatively limited, but continue to accumulate over the last years.

LESSONS LEARNED FROM ADULT STUDIES

A factor leading to potential confusion in the interpretation of colistin studies is the way of quantification of CMS doses; 3 ways have been used to express CMS doses
administered, as (1) international unit of CMS, (2) milligram of CMS and (3) milligram of colistin base activity. One milligram of CMS is equivalent to 12,500 IU of CMS, and 1 mg of colistin base activity is equivalent to 2.66 mg of CMS. A useful equation is: 1,000,000 IU of CMS = 80 mg CMS = 30 mg of colistin base activity.\(^1\)

After intravenous administration of CMS, colistin levels are higher in the liver, kidneys, heart and muscles but significantly lower in the bones, cerebrospinal fluid (CSF), lung parenchyma and pleural cavity.\(^6\) The pharmacokinetic/pharmacodynamic parameter that best correlates with colistin efficacy is the ratio: unbound colistin plasma concentration/minimum inhibitory concentration area under the curve ([AUC]/MIC).\(^1\) In a mouse thigh model of *P. aeruginosa* or *A. baumannii* infection, target values of [AUC]/MIC for 2 log_{10} kill were 7.4–17.6; in the *A. baumannii* infection, target values of [AUC]/MIC are 25–100 and 62.5–150 for several *A. baumannii* isolates.\(^2\) Evidence for clinical benefit of combination therapy is still unclear, but prospective randomized controlled trials (RCTs) are needed to establish a standard of care.\(^4,5\)

**PHARMACOKINETICS OF COLISTIN IN CHILDREN AND NEONATES**

Currently recommended pediatric CMS doses by European Medicines Agency are 75,000–150,000 IU/kg/d and by Food and Drug Administration are 83,000–166,000 IU/kg/d (2.5–5 mg/kg/d of colistin base in 2–4 divided doses).\(^9\) Higher CMS doses have been used/proposed for patients with cystic fibrosis both in Europe (150,000 IU/kg/d) and in United States (250,000 IU/kg/d). However, there is still a paucity of pharmacokinetic data for children and neonates generated by modern, valid, assays.\(^1\)

Using liquid chromatography-tandem mass spectrometry, peak and trough serum and CSF colistin levels were determined in patients 1½ months to 14 years old who carried an external ventricular drainage and received CMS at 60,000–225,000 IU/kg/d in 3 divided doses for Gram-negative bacterial infections.\(^10\) Only in 1 of 5 CMS courses studied (14-year-old receiving 225,000 IU/kg/d), serum concentrations exceeded the 2 μg/mL susceptibility breakpoint. In younger patients, 5½ month and 5½ years old, administration of 200,000 IU/kg/d of CMS resulted in mean peak levels of 1.33 and 1.60 μg/mL, respectively. These limited data suggest that doses higher than those currently recommended may be needed to treat infections caused by isolates with MIC >1 μg/mL in young children. In the absence of meningeval inflammation, colistin levels in CSF ranged between 3% and 19% of serum peak levels, with absolute values <0.2 μg/mL. In the presence of meningitis (5½-month-old patient), colistin CSF concentrations reached 0.5 μg/mL, a potentially therapeutic level only for very susceptible isolates (with MIC <0.5 μg/mL). Therefore, intravenous CMS administration may be insufficient for CNS infections caused by less susceptible isolates, and intraventricular/intrathecal administration may be required.\(^10\)

Using HPLC, Nakwan et al\(^11\) studied colistin pharmacokinetics after a single CMS dose of 150,000 IU/kg in 7 neonates of median gestational age 38 weeks and median age 13 days, suffering from bacteremia or ventilator-associated pneumonia (VAP). The mean (±SD) Cmax was 3.0 ± 0.7 μg/mL, the AUC was 25.3 ± 10.4 μg h/mL and half-life (t\(_{1/2}\)) was 9.0 ± 6.5 hours. The calculated average concentration at steady state (Cave,ss) was 1.1 ± 0.43 μg/mL. Six hours after administration, plasma colistin concentration was <2 μg/mL in all neonates and <1 μg/mL in 5 of them. The authors concluded that the above dose resulted in suboptimal colistin concentrations and higher doses should be studied.\(^11\)

Pulmonary and systemic pharmacokinetics of colistin was also investigated using HPLC after a single dose of 120,000 IU/kg of nebulized CMS in 6 mechanically ventilated neonates (median gestational age: 38 weeks) with VAP.\(^12\) The mean Cmax of colistin in tracheal aspirate was 24.0 ± 8.2 μg/mL, AUC was 147.6 ± 53.5 μg h/mL and t\(_{1/2}\) was 9.8 ± 5.5 hours. Colistin concentrations in tracheal aspirate exceeded 2 μg/mL up to 12 hours after nebulization in 5 of 6 neonates and up to 24 hours in 3 of 6 neonates. Mean plasma colistin Cmax was 0.59 ± 0.35 μg/mL. The authors concluded that nebulization with 120,000 IU of CMS resulted in high tracheal aspirate and low plasma concentrations of colistin; however, a twice-daily dosing regimen might be more appropriate.\(^12\)

**SAFETY AND EFFICACY OF COLISTIN IN CHILDREN AND NEONATES**

Recent publications on the clinical use of CMS in pediatric patients include non-comparative, mostly retrospective, patient series.\(^13–18\) Almost all of these studies analyze a mixed group of patients, from young infancy to adolescence, without age stratification with regards to dosing, adverse events and efficacy. This is a significant drawback of these studies, as all of these parameters may be significantly affected by age. Most common indications for CMS administration were bacteremia, lung infection (often VAP) and less frequently skin and soft tissue, urinary tract and CNS infections. Almost always there was concomitant administration of other agents active against Gram-negative bacteria, such as carbapenems, aminoglycosides or fluoroquinolones, which precludes a net assessment of CMS efficacy.\(^13–18\)

CMS dosage employed ranged between 50,000 and 120,000 IU/kg/d in 3 divided doses) without loading dose, for most of the patients included in the studies mentioned above. In some cases however, higher doses have been used, ranging from 166,000–225,000 IU/kg/d in cystic fibrosis patients, doses up to 250,000 IU/kg/d have been administered.\(^16\) A favorable clinical outcome was observed in >70% of patients in most of the studies.\(^15,17,18\) With
the exception of a US multicenter series demonstrating clinical cure in 45.9% of cases and crude mortality of 25%. It should be noted, however, that the US study included older children (median age: 12.2 years) compared with most of the other studies in which median patient age ranged between 3 months and 8 years. With regards to adverse events, reversible nephrotoxicity was observed in 3%–10% of patients in most studies; in many cases, patients were concomitantly receiving other nephrotoxic agents. A higher incidence (22%) of nephrotoxicity was recorded in the US multicenter series, which might be attributed to older patient age. In fact, the risk for developing nephrotoxicity in children ≥13 years old was approximately 7 times that of younger children, even after adjusting for additional nephrotoxic agents. Reversible neurotoxicity (mainly paresthesias and headache) was rarely observed in older children treated with CMS. Limited studies have focused on neonates (including preterm, of various gestational age and birth weight) treated with CMS for bacteremia or VAP caused by A. baumannii or other organisms. CMS doses ranged between 30,000 and 75,000 IU/kg/d, and other antibiotics were co-administered in almost all cases. A favorable clinical response was seen in >75% of neonates. Creatinine levels were infrequently affected by CMS treatment; however, in a significant proportion of patients, electrolyte disturbances were observed, mainly hypomagnesemia and hypokalemia, which required supplementation with magnesium and potassium, respectively. It appears prudent to monitor serum electrolytes, including magnesium, in neonates receiving CMS.

As in adult patients, infections of the CNS or lung may require administration of CMS through other routes. A dose of 125,000 IU of CMS has been employed for intraventricular administration in 2 children and 1 neonate with CNS infection. Inhaled CMS has been used as adjunctive therapy (166,000 IU/kg twice daily) or monotherapy (1,000,000 IU twice daily) in preterm neonates with VAP, with very good response and no adverse events.

CONCLUSIONS

Colistin is one of the very few agents still active against carbapenem-resistant Gram-negative bacteria. It has complicated pharmacokinetics with high inter-patient variability and a narrow therapeutic window. There is a paucity of pharmacokinetic data for pediatric patients and a number of questions that need to be addressed, such as the role of combination therapy and therapeutic drug monitoring. Plasmid-encoded colistin resistance, now spread all over the world, might be attributed to older patient age. In fact, the risk for developing nephrotoxicity in children ≥13 years old was approximately 7 times that of younger children, even after adjusting for additional nephrotoxic agents. Reversible neurotoxicity (mainly paresthesias and headache) was rarely observed in older children treated with CMS.

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