AJKD

Narrative Review

Colistin Use in Patients With Reduced Kidney Function

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Colistin (polymyxin E) is a mainly concentration-dependent bactericidal antimicrobial active against multidrug-resistant Gram-negative bacteria. After being abandoned over the past 30 years due to its neuro- and nephrotoxicity, colistin has been reintroduced recently as a last-resort drug for the treatment of multidrug-resistant Gram-negative bacteria infections in combination with other antimicrobials. Unfortunately, although renal toxicity is a well-known dose-related adverse effect of colistin, relatively few studies are currently available on its peculiar pharmacodynamic/pharmacokinetic properties in clinical settings at high risk for drug accumulation, such as acute or chronic kidney disease. In these specific contexts, the risk for underdosing is also substantial because colistin can be easily removed by dialysis/hemofiltration, especially when the most efficient modalities of renal replacement therapy (RRT) are used in critically ill patients. For this reason, recent recommendations in patients undergoing RRT have shifted toward higher dosing regimens, and therapeutic drug monitoring is advised. This review aims to summarize the main issues related to chemical structure, pharmacodynamics/pharmacokinetics, and renal toxicity of colistin. Moreover, recent data and current recommendations concerning colistin dosing in patients with reduced kidney function, with special regard to those receiving RRT such as dialysis or hemofiltration, are also discussed.

Am J Kidney Dis. ■(■):■-■. © *2016 by the National Kidney Foundation, Inc.*

INDEX WORDS: Acute kidney injury (AKI); colistin; colistin methanesulfonate; polymyxin E; continuous renal replacement therapies (CRRTs); renal toxicity; nephrotoxicity; chronic kidney disease (CKD); critical illness; dialysis; hemofiltration; kidney function; colistin pharmacokinetics; colistimethate; therapeutic drug monitors.

Colistin is a mainly concentration-dependent bactericidal antibiotic active against multidrug-resistant Gram-negative bacteria (*Pseudomonas aeruginosa, Acinetobacter baumannii,* carbapenemase-producing Enterobacteriaceae, etc)[1,2] originally introduced in 1958 and subsequently abandoned because of its toxicity.[3] Colistin is now increasingly used as a last-resort drug for multidrug-resistant Gram-negative bacteria infections, that is, ventilator-associated pneumonia, urinary tract infections, bacteremia, central catheter–associated sepsis, peritonitis, and meningitis.[3,4]

Colistin pharmacokinetics still remain ill defined, especially in clinical settings at high risk for both over- and underdosing, such as chronic kidney disease (CKD) and acute kidney injury (AKI), especially when renal replacement therapies (RRTs) are needed.

This narrative review is aimed at describing pharmacodynamic/pharmacokinetic issues, dosing recommendations, and toxicity of colistin, as well as the changes in its pharmacokinetic properties associated with reduced kidney function (AKI and CKD), with or without RRT need.

SEARCH STRATEGY

A review of the English language literature was performed to identify relevant articles describing pharmacodynamics/pharmacokinetics, renal toxicity, and dosing adjustments for colistin in AKI, CKD, and RRT. We searched PubMed, Embase, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), Web of Science, and Cochrane databases for relevant articles using the following search terms: "acute kidney injury OR acute renal failure," "chronic kidney disease," "continuous venovenous hemofiltration, CVVH," "continuous venovenous hemodialysis, CVVHD," "continuous renal replacement therapy, CRRT," "colistin," "colistin methanesulphonate," "colistimethate," "critical illness," "dialysis OR hemofiltration," "intravenous," "nephrotoxicity," "neurotoxicity," "peritoneal dialysis," "pharmacokinetics," "pharmacodynamics," "renal

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Received December 30, 2015. Accepted in revised form March 21, 2016.

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0272-6386

http://dx.doi.org/10.1053/j.ajkd.2016.03.421

replacement therapy," "therapeutic drug monitoring," and "toxicity." Medical Subject Heading (MeSH) terms were used to enhance electronic searches. Additional studies of interest were identified by hand searches of reference lists. Studies including patients younger than 18 years, case reports, or conference proceedings were excluded. The search was last updated on March 13, 2016.

CHEMICAL STRUCTURE OF COLISTIN

Colistin (polymyxin E) is produced by strains of *Bacillus polymyxa* subspecies *colistinus*.[3,4] Colistin is a multicomponent lipopeptide that contains colistin A and colistin B, which only vary in the fatty acid chain attached to the cyclic decapeptide moiety of the drug. Its molecular weight is 1,163 Da, and it is an amphiphilic molecule: its hydrophilic properties arise from the polycationic cyclic peptide and the hydrophobic portion is the fatty acyl tail (Fig 1).[4] Colistin is primarily distributed in the extracellular fluid with limited penetration in the intracellular compartment and reaches adequate concentrations in many tissues (liver, kidney, skeletal muscle, heart, and lungs), but does not cross the blood-brain barrier when intact.[4] The drug is commercially available as its prodrug colistimethate sodium (colistin methanesulfonate sodium; molecular weight, 1,743 Da), also administered by the intramuscular route and nebulization. As a sulfate salt, colistin can only be administered orally, for intestinal decontamination, or as a topical drug, for cutaneous infections. Colistimethate is a variable mixture of the methanesulfonic sodium salts of colistin A and colistin B that after administration spontaneously converts by hydrolysis to colistin (20%-30% of colistin methanesulfonate sodium dose).[4] Bactericidal activity of colistin is considered mainly concentration dependent, with a mild post-antibiotic effect at higher concentrations; however, colistin is classified as both a concentration- and time-dependent antibiotic.[5] Given the toxicity of the parental antibiotic, colistin is administered as its prodrug colistin methanesulfonate sodium, by intravenous delivery or nebulization. Thus, the available brands for parenteral colistin therapy contain colistin methanesulfonate sodium. International units or milligrams of colistin methanesulfonate sodium are used for dosing in Europe, the United Kingdom, and India, whereas in the remaining regions, including North and South America, Southeast Asia, and Australia, milligrams of colistin base activity are used. One million international units of colistin methanesulfonate sodium corresponds to 80 mg and equals 30 mg of colistin base activity.

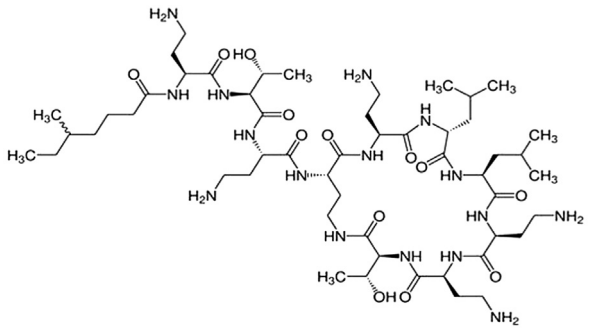

Figure 1. Chemical structure of colistin (polymyxin E).

PHARMACODYNAMICS OF COLISTIN

Colistin in water-containing solutions acquires cationic and surfactant properties, thus increasing the permeability of the Gram-negative bacteria cellular envelope by inducing a loss of integrity of the cytoplasmic membrane.[3,4] The polycationic region of colistin interacts with the anionic region of lipopolysaccharide, the major component of the outer Gram-negative bacterial membrane, displacing divalent calcium and magnesium cations that normally stabilize the external lipopolysaccharide leaflet, with secondary membrane instability and cell lysis. The antibacterial action of colistin is rapid (1-2 hours) on both quiescent and actively replicating bacteria, and this partially explains the delay between colistin administration and the development of bacterial resistance. Also, direct binding to the lipid portion of the lipopolysaccharide molecule, with ensuing endotoxin neutralization, may contribute to the antibacterial effect of colistin by direct antiendotoxin activity.

SPECTRUM OF BACTERIAL SUSCEPTIBILITY AND BACTERIAL RESISTANCE TO COLISTIN

Colistin has a limited spectrum of antimicrobial activity (Table 1).[3,4] The reference method recommended by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) to evaluate colistin sensitivity remains the broth microdilution method: according to EUCAST criteria, sensitivity and resistance break points are $\leq$2 mg/L and $>$2 mg/L for Enterobacteriaceae and $\leq$4 mg/L and $>$4 mg/L for *P aeruginosa*, respectively.[6] Resistance against colistin has been rarely detected[7] because of its mechanism of action and its uncommon use in clinical practice in the past. Resistance to polymyxins is usually attributed to chromosomal mutations leading to modification of lipid A and lipopolysaccharide composition with consequent reduction of affinity for colistin. However, recently, horizontal gene transfer (ie, plasmid-mediated resistance) between Enterobacteriaceae has been reported in China in both farm animals and humans.[8] The usual recommendation is to administer colistin not in single-drug antibiotic