Colistin: The phoenix arises

JM Conly MD[1], BL Johnston MD[2]

The polymyxins were discovered in the 1940s and represent a group of closely related polypeptide antibiotics obtained from *Bacillus polymyxa*, which was originally isolated from soil (1,2). Although they have been used extensively worldwide in topical otic and ophthalmic solutions for decades, the intravenous formulations were gradually abandoned in most parts of the world in the early 1980s because of the reported high incidence of nephrotoxicity (3-5). As a result, the use of polymyxin preparations has been mainly restricted to the treatment of lung infections due to multidrug-resistant (MDR) gram-negative bacteria in patients with cystic fibrosis (6,7). The emergence of bacteria resistant to most classes of commercially available antibiotics and the shortage of novel antimicrobial agents with activity against gram-negative microorganisms have led to the reemergence of polymyxins as a valuable addition to the therapeutic armamentarium. It was thus considered timely to review colistin and its emerging role in managing infections due to MDR gram-negative bacteria.

The polymyxins are cyclic basic polypeptides that consist of five chemically different compounds (polymyxins A to E) and are characterized by poor diffusibility, a molecular weight of approximately 1100, and activity directed predominantly against gram-negative aerobes. All but polymyxin B and polymyxin E are too toxic for use in humans. Polymyxin E is also known commonly as colistin. Both polymyxin B and polymyxin E contain D- and L-amino acids, a heptapeptide ring, 2,4-diaminobutyric acid and a fatty acid attached through an amide bond (2). The polymyxins are surface active amphipathic agents, which interact strongly with phospholipids within the cell membrane and act in a detergent-like fashion to disrupt the structure of the cell membrane (1,8). The initial association of colistin with the bacterial membrane occurs through interactions between the cationic polypeptide (colistin) and the anionic lipopolysaccharide within the outer membrane of the gram-negative bacteria, leading to derangement of the cell membrane. Colistin displaces magnesium and calcium (ions that normally stabilize the lipopolysaccharide molecules) from the negatively charged lipopolysaccharide, leading to a loss of integrity of the membrane and an increase in the permeability of the cell envelope, leakage of cell contents, and subsequently, cell death (9,10). The polymyxins act immediately in this process of disrupting the osmotic integrity of the cell membrane and are considered bactericidal agents. Polymyxin B and colistin also avidly bind to the lipid A portion of endotoxin in the outer membrane of gram-negative bacteria and inactivates the molecule (11). Resistance to colistin may occur through mutation or adaptation mechanisms. Mutation is low-level and does not depend on the presence of the antibiotic, whereas adaptation is dependent on the presence of the antibiotic. Studies of polymyxin-resistant *Pseudomonas aeruginosa* strains have suggested that alterations in the outer membrane of the bacterial cell are related to the development of resistance (12-14). Other mechanisms of resistance may also occur, with a recent study demonstrating in *Yersinia* species that an efflux pump/potassium system may be associated with resistance to polymyxin B (15). Almost complete cross-resistance exists between colistin and polymyxin B (12,13). Although considered uncommon, heteroresistance to colistin was recently observed in 15 of 16 'colistin-susceptible' clinical isolates of *Acinetobacter baumannii*, suggesting that colistin-resistant *A baumannii* may be observed in the setting of suboptimal dosing (16).

The polymyxins are highly soluble in water and poorly soluble in organic solvents. There are two forms of colistin available commercially: colistin sulfate, which is used in topical preparations for the treatment of bacterial skin infections or administered orally in the form of tablets or syrup for bowel decontamination, and colistimethate sodium (also known as colistin methanesulfonate sodium), which is used for parenteral administration either intravenously or intramuscularly. Both colistin sulfate and colistimethate sodium may be administered by nebulization. The basic chemistry, pharmacology, clinical applications, pharmacokinetics and pharmacodynamics of these two forms of colistin are quite different, however, and these differences have important implications (17-21). Colistimethate sodium is a nonactive prodrug, and after parenteral administration, colistin is formed in vitro and in vivo (18,19). In aqueous solutions, the colistimethate sodium is hydrolyzed and forms a complex mixture of partially sulfomethylated derivatives and colistin (22). Under different conditions, different proportions of colistimethate sodium are hydrolyzed to colistin. Colistin is more stable than colistimethate sodium in human plasma. A recent in vitro study demonstrated that 31.2% of colistimethate sodium in human plasma was hydrolyzed to colistin in 4 h at 37°C (23). Whereas colistimethate sodium is renally eliminated and the urinary excretion involves renal tubular secretion, colistin is eliminated predominantly by the nonrenal route with very extensive renal tubular reabsorption (18). Approximately 60% of colistimethate sodium is excreted as unchanged drug in the urine during the first 24 h after dosing (18-21). After parenteral administration of colistimethate sodium in patients with cystic fibrosis, the plasma half-life of colistimethate sodium (124±52 min) is approximately one-half that of the colistin

[1]*Departments of Pathology and Laboratory Medicine, Medicine, and Microbiology and Infectious Diseases, Centre for Antimicrobial Resistance, University of Calgary, Calgary, Alberta;* [2]*Queen Elizabeth II Health Sciences Centre and Dalhousie University, Halifax, Nova Scotia*
Correspondence: Dr JM Conly, Foothills Medical Centre, 1403–29 Street South, Calgary, Alberta T2N 2T9. Telephone 403-944-8222, fax 403-944-1095, e-mail jconly@ucalgary.ca
Received and accepted for publication July 24, 2006

generated from it (251±79 min) (19). No biliary excretion has been reported in humans. Colistin is not absorbed through intact cutaneous surfaces and is not absorbed from the gastrointestinal tract. Both colistin sulfate and colistimethate sodium exhibit their bactericidal activity in a concentration-dependent manner (21).

Because of the differences between colistimethate and colistin, interpretation of a minimal inhibitory concentration is dependent on which entity has been used. In January 2005, the United States Clinical and Laboratory Standards Institution provided information for testing quality control strains against colistin (24). The currently available breakpoints for colistin susceptibility are based on colistin sulfate (2 mg/L or less as the susceptibility breakpoint, and more than 2 mg/L as the resistance breakpoint). The antimicrobial activity of colistin is similar to that of polymyxin B and is restricted to gram-negative bacteria, including *P aeruginosa*, *Acinetobacter* species, *Enterobacter-Klebsiella* tribe, *Escherichia coli*, *Salmonella* and *Shigella* species, *Citrobacter* species, *Yersinia pseudotuberculosis*, *Morganella morganii* and *Haemophilus influenzae* (2,25). Colistin has also been shown to possess considerable in vitro activity against *Stenotrophomonas maltophilia* (25,26). Colistin and polymyxin B, however, do not have activity against *Proteus*, *Providencia*, *Serratia* species, *Pseudomonas mallei*, *Burkholderia cepacia*, *Brucella* species, most gram-positive bacteria, gram-negative cocci, anaerobes, fungi and parasites (2,25). Polymyxins have been demonstrated to exhibit synergy against gram-negative organisms in combination with a number of other antimicrobials, including tetracyclines, chloramphenicol and beta-lactams (1). The in vitro activity of polymyxins is neutralized by the presence of divalent cations at physiological concentration in body fluids. There is no cross-resistance to other classes of antibiotics (2,25).

Colistin has been used for many years as an inhalational agent in patients with cystic fibrosis to reduce the effects of colonization by *P aeruginosa* (27,28). Most recently, intravenous colistin (as colistimethate sodium) has been used for the treatment of infections caused by MDR gram-negative bacteria, and this is the setting in which a resurgence of interest in this agent has occurred (29-37). These reported studies are not from controlled clinical trials and, thus, are susceptible to all of the biases associated with observational and case series analyses. Nonetheless, the use of colistin has often been in the setting where no other therapies are available. The dosage of intravenous colistin recommended by manufacturers in the presence of normal renal function is 2.5 mg/kg to 5 mg/kg (31,250 IU/kg to 62,500 IU/kg) per day, divided into two to four equal doses (1 mg of colistin equals 12,500 IU). However, the recommended dosage in the United Kingdom is 4 mg/kg to 6 mg/kg per day, in three divided doses for adults and children with a body weight of 60 kg or lighter, and 80 mg to 160 mg every 8 h for those with a body weight heavier than 60 kg. There are also reports of higher dosing ranges of up to 720 mg per day in three divided doses administered intravenously (34,38). The most common adverse effects of colistin therapy that have been reported are nephrotoxicity and neurotoxicity. Early experience with colistin revealed an incidence of nephrotoxicity as high as 20.2% (39), but more recent studies in varying patient groups have suggested that this incidence is lower (29,37). The frequency of colistin-associated neurotoxicity reported in earlier literature was approximately 7%, with paresthesiae constituting the main neurotoxicity (39). Additional studies will be required to determine whether the frequency of neurotoxicity and nephrotoxicity, in an era with closer monitoring and improved supportive care, are as frequent as reported previously.

As the use of colistin increases, driven by clinical need, it will become increasingly important to carefully evaluate its efficacy, pharmacokinetic and pharmacodynamic properties, development of resistance and toxicity. Given that colistin was developed over 40 years ago, there are significant gaps in our knowledge and expertise in the use of this agent. An entire generation of trainees has no experience with its use, and with the dearth of new antibiotic agents, it cannot be overemphasized that we must find more effective means of using our existing antibiotics, including older agents such as colistin.

REFERENCES

1. Hoeprich PD. The polymyxins. Med Clin North Am 1970;54:1251-65.
2. Storm DR, Rosenthal KS, Swanson PE. Polymyxin and related peptide antibiotics. Annu Rev Biochem 1977;46:723-63.
3. Brown JM, Dorman DC, Roy LP. Acute renal failure due to overdosage of colistin. Med J Aust 1970;2:923-4.
4. Koch-Weser J, Sidel VW, Federman EB, Kanarek P, Finer DC, Eaton AE. Adverse effects of sodium colistimethate. Manifestations and specific reaction rates during 317 courses of therapy. Ann Intern Med 1970;72:857-68.
5. Ryan KJ, Schainuck LI, Hickman RO, Striker GE. Colistimethate toxicity. Report of a fatal case in a previously healthy child. JAMA 1969;207:2099-101.
6. Conway SP, Pond MN, Watson A, Etherington C, Robey HL, Goldman MH. Intravenous colistin sulphomethate in acute respiratory exacerbations in adult patients with cystic fibrosis. Thorax 1997;52:987-93.
7. Cunningham S, Prasad A, Collyer L, Carr S, Lynn IB, Wallis C. Bronchoconstriction following nebulised colistin in cystic fibrosis. Arch Dis Child 2001;84:432-3.
8. Evans ME, Feola DJ, Rapp RP. Polymyxin B sulfate and colistin: Old antibiotics for emerging multiresistant gram-negative bacteria. Ann Pharmacother 1999;33:960-7.
9. Davis SD, Iannetta A, Wedgwood RJ. Activity of colistin against *Pseudomonas aeruginosa*: Inhibition by calcium. J Infect Dis 1971;124:610-2.
10. Schindler M, Osborn MJ. Interaction of divalent cations and polymyxin B with lipopolysaccharide. Biochemistry 1979;18:4425-30.
11. Gough M, Hancock RE, Kelly NM. Antiendotoxin activity of cationic peptide antimicrobial agents. Infect Immun 1996;64:4922-7.
12. Moore RA, Chan L, Hancock RE. Evidence for two distinct mechanisms of resistance to polymyxin B in *Pseudomonas aeruginosa*. Antimicrob Agents Chemother 1984;26:539-45.
13. Moore RA, Hancock RE. Involvement of outer membrane of *Pseudomonas cepacia* in aminoglycoside and polymyxin resistance. Antimicrob Agents Chemother 1986;30:923-6.
14. Gunn JS, Lim KB, Krueger J, et al. PmrA-PmrB regulated genes necessary for 4-aminoarabinose lipid A modification and polymyxin resistance. Mol Microbiol 1998;27:1171-82.
15. Bengoechea JA, Skurnik M. Temperature-regulated efflux pump/potassium antiporter system mediates resistance to cationic antimicrobial peptides in *Yersinia*. Mol Microbiol 2000;37:67-80.
16 Li J, Rayner CR, Nation RL, et al. Heteroresistance to colistin in multidrug-resistant *Acinetobacter baumannii*. Antimicrob Agents Chemother 2006;50:2946-50.
17. Li J, Nation RL, Milne RW, Turnidge JD, Coulthard K. Evaluation of colistin as an agent against multi-resistant gram-negative bacteria. Int J Antimicrob Agents 2005;25:11-25.
18. Li J, Milne RW, Nation RL, Turnidge JD, Smeaton TC, Coulthard K. Pharmacokinetics of colistin methanesulphonate and colistin in rats following an intravenous dose of colistin methanesulphonate. J Antimicrob Chemother 2004;53:837-40.

19. Li J, Coulthard K, Milne R, et al. Steady-state pharmacokinetics of intravenous colistin methanesulphonate in patients with cystic fibrosis. J Antimicrob Chemother 2003;52:987-92.
20. Li J, Rayner CR, Nation RL, et al. Pharmacokinetics of colistin methanesulfonate and colistin in a critically ill patient receiving continuous venovenous hemodiafiltration. Antimicrob Agents Chemother 2005;49:4814-5.
21. Li J, Turnidge J, Milne R, Nation RL, Coulthard K. In vitro pharmacodynamic properties of colistin and colistin methanesulfonate against *Pseudomonas aeruginosa* isolates from patients with cystic fibrosis. Antimicrob Agents Chemother 2001;45:781-5.
22. McMillan FH, Pattison IC. Sodium colistimethate. I. Dissociations of aminomethanesulfonates in aqueous solution. J Pharm Sci 1969;58:730-7.
23. Li J, Milne RW, Nation RL, Turnidge JD, Coulthard K. Stability of colistin and colistin methanesulfonate in aqueous media and plasma as determined by high-performance liquid chromatography. Antimicrob Agents Chemother 2003;47:1364-70.
24. Clinical and Laboratory Standards Institution. Performance standards for antimicrobial susceptibility testing. Fifteenth information supplement (M100-S15). Clinical and Laboratory Standards Institution: Pennsylvania, 2005.
25. Catchpole CR, Andrews JM, Brenwald N, Wise R. A reassessment of the in-vitro activity of colistin sulphomethate sodium. J Antimicrob Chemother 1997;39:255-60.
26. Hogardt M, Schmoldt S, Gotzfried M, Adler K, Heesemann J. Pitfalls of polymyxin antimicrobial susceptibility testing of *Pseudomonas aeruginosa* isolated from cystic fibrosis patients. J Antimicrob Chemother 2004;54:1057-61.
27. Littlewood JM, Koch C, Lambert PA, et al. A ten year review of colomycin. Respir Med 2000;94:632-40.
28. Conway SP, Brownlee KG, Denton M, Peckham DG. Antibiotic treatment of multidrug-resistant organisms in cystic fibrosis. Am J Respir Med 2003;2:321-32.
29. Garnacho-Montero J, Ortiz-Leyba C, Jimenez-Jimenez FJ, et al. Treatment of multidrug-resistant *Acinetobacter baumannii* ventilator-associated pneumonia (VAP) with intravenous colistin: A comparison with imipenem-susceptible VAP. Clin Infect Dis 2003;36:1111-8.
30. Al-Aloul M, Miller H, Alapati S, Stockton PA, Ledson MJ, Walshaw MJ. Renal impairment in cystic fibrosis patients due to repeated intravenous aminoglycoside use. Pediatr Pulmonol 2005;39:15-20.
31. Kasiakou SK, Fragoulis K, Tzagarakis G, Mistidis P, Kapaskelis A, Falagas ME. Cure of multidrug-resistant *Acinetobacter baumannii* fixation device-related orthopedic infections in two patients with intravenous colistin. Microb Drug Resist 2005;11:287-9.
32. Fulnecky EJ, Wright D, Scheld WM, Kanawati L, Shoham S. Amikacin and colistin for treatment of *Acinetobacter baumannii* meningitis. J Infect 2005;51:249-51.
33. Linden P, Kusne S, Coley K, Fontes P, Kramer D, Paterson D. Use of parenteral colistin for the treatment of serious infection due to antimicrobial-resistant *Pseudomonas aeruginosa*. Clin Infect Dis 2003;37:154-60.
34. Markou N, Apostolakos H, Koumoudiou C, et al. Intravenous colistin in the treatment of sepsis from multiresistant gram-negative bacilli in critically ill patients. Crit Care 2003;7:R78-83.
35. Michalopoulos A, Kasiakou SK, Rosmarakis ES, Falagas ME. Cure of multidrug-resistant *Acinetobacter baumannii* bacteremia with continuous intravenous infusion of colistin. Scand J Infect Dis 2005;37:142-5.
36. Berlana D, Llop JM, Fort E, Badia MB, Jodar R. Use of colistin in the treatment of multiple-drug-resistant gram-negative infections. Am J Health Syst Pharm 2005;62:39-47.
37. Levin AS, Barone AA, Penco J, et al. Intravenous colistin as therapy for nosocomial infections caused by multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. Clin Infect Dis 1999;28:1008-11.
38. Michalopoulos A, Tsiodras S, Rellos K, Mentzelopoulos S, Falagas ME. Colistin treatment in patients with ICU-acquired infections caused by multiresistant gram-negative bacteria: The renaissance of an old antibiotic. Clin Microbiol Infect 2005;11:115-21.
39. Koch-Weser J, Sidel VW, Federman EB, Kanarek P, Finer DC, Eaton AE. Adverse effects of sodium colistimethate. Manifestations and specific reaction rates during 317 courses of therapy. Ann Intern Med 1970;72:857-68.