

## Attention to Colistin Dose: A Case Report of Rare Neurotoxic Adverse Effects

### Kolistin Dozuna Dikkat: Nadir Nörotoksik Yan Etkilerin Görüldüğü Bir Olgu Sunumu

Nilay Şengül SAMANCI,<sup>a</sup>  
Abdülkadir ERGEN,<sup>a</sup>  
Meryem TAHMAZ,<sup>a</sup>  
Egemen CEBECİ,<sup>b</sup>  
Savaş ÖZTÜRK<sup>b</sup>

Clinics of  
<sup>a</sup>Internal Medicine,  
<sup>b</sup>Nephrology,  
Haseki Training Research Hospital,  
İstanbul

Geliş Tarihi/Received: 16.01.2017  
Kabul Tarihi/Accepted: 04.04.2017

Yazışma Adresi/Correspondence:  
Nilay ŞENGÜL SAMANCI  
Haseki Training Research Hospital,  
Clinic of Internal Medicine, İstanbul,  
TURKEY/TÜRKİYE  
nilaysengulsamanci@gmail.com

2013 15<sup>th</sup> National Internal Medicine Congress  
(2-6 October 2013, Antalya) is presented as a  
case summary.

**ABSTRACT** Colistin is a polymyxin antibiotic that is used for the treatment of multidrug-resistant Gram-negative bacteria. The most important side effects of intravenous colistin is nephrotoxicity and neurotoxicity. Neurotoxicity is seen much less frequently (<7%) than nephrotoxicity. Because of the ideal dose for colistin remains uncertain and loading dose is calculated independently of creatinine clearance in patients with kidney disease its safety is unclear. In this paper we present a case of colistin neurotoxicity in a patient with complaints of weakness, dizziness, visual disturbances, ataxia and peripheral paresthesia 5-6 hours after loading dose who has kidney disease. Colistin treatment was stopped, ascorbic acid was added to the treatment and 2-3 hours after hemodialysis, his neurotoxicity symptoms disappeared.

**Keywords:** Adverse effects; colistin; polymyxins

**ÖZET** Kolistin, çoklu ilaç dirençli Gram-negatif bakterilerin tedavisinde kullanılan bir polimiksin antibiyotiktir. İntravenöz kolistinin en önemli yan etkileri nefrotoksisite ve nörotoksisitedir. Nörotoksisite, nefrotoksisiteye göre daha az (<7%) görülür. Kolistin için ideal doz belirsiz olduğundan ve yükleme dozu böbrek hastalığı olan hastalarda kreatinin klirensinden bağımsız olarak hesaplandığından, güvenliği açık değildir. Bu yazıda böbrek hastalığı olan bir hastaya yükleme dozundan 5-6 saat sonra ortaya çıkan zayıflık, baş dönmesi, görme bozuklukları, ataksi ve periferik paresteziye ilişkin bir kolistin nörotoksik şikayeti sunulmuştur. Hastanın kolistini kesilmiş, tedaviye ascorbic asit eklenmiş ve hemodiyalize alınan hastanın 2-3 saat sonra nörotoksisite semptomları kaybolmuştur.

**Anahtar Kelimeler:** İstenmeyen etkiler; kolistin; polimiksinler

Polymyxin antibiotics are necessarily preferable in the treatment of problematic bacteria such as multi-drug resistance *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and carbapenemase-producing enteric microorganism.<sup>1</sup> In practice, only polymyxin E (colistin) and polymyxin B are used. There are two major adverse effects related to colistin therapy. Nephrotoxicity is one of the generally observed adverse effects following intravenous treatment of colistin. Neurotoxicity is a less common adverse effect than nephrotoxicity. Neurotoxic side effects are generally mild and reversible after stopping the treatment.<sup>2</sup>

The ideal dose for colistin remains uncertain. Colistin loading dose is calculated independently of creatinine clearance (CCr). Our purpose is to discuss this entity.

## CASE REPORT

Forty-five year old male patient was admitted to our clinic with complaints of fever, nausea and vomiting for 6 days. In his medical history he had type 2 diabetes mellitus for 11 years. His physical examination revealed bilateral costovertebral angle tenderness and his fever was 38.5° C, blood pressure was 100/70. Neurological examination was normal. Creatinine: 7.66 mg/dl, Urea: 234 mg/dl, Wbc:15300, Neu: 12800, Hb: 8 g/dl, Plt: 162000, sedimentation: 107/hr, CRP: 258(0-5) have been found in the laboratory findings. Urine analysis revealed 40 leukocyte, 5 erythrocytes on dipstick. It's learned that the value of creatinine was 2.8 one week ago. Abdominal ultrasonography findings showed grade 2 pelvicaliectasis, perirenal minimal free fluid and large swollen kidney with an increased anechoic corticomedullary area. It was consistent with pyelonephritis. Empirical antibiotic treatment was started after blood and urine cultures were taken. Two days later his creatinine and urea levels decreased to 5.42 mg/dl, 205 mg/dl. Blood and urine cultures were positive for *Klebsiella pneumoniae* and antibiograms reported amikacin and colistin susceptibility for *Klebsiella pneumoniae*. Because of amikacin cannot be used alone we used colistin for treatment. Colistin loading dose was calculated independently of creatinine clearance (CCr) according the formula colistin  $C_{ss,avg}$  target (2,5 mg) x 2.0 body weight (kg). Creatinine clearance was 11 ml/min/1,73 m<sup>2</sup> and maintenance dose was calculated 2x58 mg according to the formula of  $(2.5 (C_{ss,avg} \text{ target}) \times (1.5 \times (CCr)+30))$ . 5-6 hours after loading dose the patient had complaints of weakness, dizziness, visual disturbances, ataxia and peripheral paresthesia. Colistin treatment stopped and it was consistent with colistin neurotoxicity. We added ascorbic acid to the treatment. When the regression is not seen in neurotoxicity symptoms, we started hemodialysis. 2-3 hours after hemodialysis, his neurotoxicity symptoms disappeared. In following 2 weeks his creatinine levels decreased to 1,89 mg/dl, definite clinical improvement was observed and the patient was discharged.

## DISCUSSION

Colistin (polymyxin E) is a polymyxin antibiotic which was first introduced in the late 1950s is used in the treatment of multidrug-resistant (MDR) Gram-negative pathogens, in particular *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*. Both colistimethate sodium (CMS) and colistin sulfate is available.<sup>1</sup> CMS is a prodrug and after intravenous administration it is hydrolyzed to make the active drug colistin.<sup>3</sup>

Colistin in our country is performed as a loading dose and maintenance dose. Loading dose is applied with the formula of  $C_{ss,avg}$  target (2.5) x 2 x body weight or 5 mg / kg (not to exceed 300 mg) in all patient categories independently of creatinine clearance. After 12 hours of the maintenance dose is started. Maintenance dose is calculated as the formula of  $2.5 \times [(1.5 \times CrCl)+30]$  and applied.<sup>4</sup>

The ideal dose for colistin remains uncertain. There is little experience with using greater loading doses of CMS than 300 mg, and the potential impact on renal function of large loading doses of CMS is not known.<sup>4</sup>

Nephrotoxicity and neurotoxicity is the most important adverse effects of intravenous colistin. Neurotoxicity is seen much less frequently (<7%) than nephrotoxicity. Neurotoxicity usually appears after prolonged use. Neurotoxic effects are usually mild and reversible after the drug was discontinued<sup>5</sup>. Neurological symptoms are dizziness, vertigo, confusion, facial and peripheral paresthesia, visual disturbances, partial deafness, hallucinations, weakness, ataxia and convulsions. In our case, many of these symptoms were observed.<sup>6</sup>

Neurotoxicity of polymyxins is also known to be dose-dependent. The mechanisms of neurotoxicity induced by polymyxins include neuromuscular blockade.<sup>7</sup> Polymyxins inhibits the release of acetylcholine to the synaptic gap. Paresthesias were the most often experienced neurological adverse effects and occurred in almost 27% and 7.3% in CMS receiving patients.<sup>6</sup> Falagas and colleagues showed in a study that in 152 patients only 4 patients were clinically diagnosed to have polyneu-

ropathy and/or myopathy.<sup>5</sup> And over the past 15 years or more no cases of apnea and neuromuscular blockade induced by polymyxins have been reported in the literature.<sup>6</sup> In a case by Patrick M Honore, while receiving intravenous colistin convulsions rapidly followed by acute respiratory muscle weakness and apnea. Toxic levels of colistin were rapidly removed by hemofiltration.<sup>8</sup>

In our case also 5-6 hours after the loading dose of colistin, neurotoxicity was observed. We added ascorbic acid to the treatment. In a study Yang Liu and colleagues examined that ascorbic acid could reduce colistin sulfate-induced neurotoxicity mediated by oxidative stress.<sup>9</sup> But the regression was not seen so we started hemodialysis. 2-3 hours after hemodialysis, his neurotoxicity symptoms disappeared.

Colistin dosages must be optimized. It is difficult to provide ideal dosing regimens and specific dosing guidelines for colistin because of the defi-

ciency of pharmacokinetic and pharmacodynamic studies.<sup>3</sup> In patients with multiorgan failure and renal insufficiency dosage alterations of colistin must get maximal efficacy and minimal toxicity. Colistin has at least 30 different mixtures of inactive derivatives. Therefore, there are difficulties to investigate the pharmacokinetics of colistin and complex to predict.<sup>10</sup> So loading dose calculating independently creatinine clearance can be discussed. And future studies on this subject will be guiding.

### Conflict of Interest

Authors declared no conflict of interest or financial support.

### Authorship Contributions

**Performed Experiments and Analyzed Data:** Nilay Şengül Samancı, Abdülkadir Ergen, Meryem Tahmaz, Egemen Cebeci, Savaş Öztürk; **Provided Critical Advice and Review of the Studies:** Savaş Öztürk and Abdülkadir Ergen; **Directed the Research and Wrote the Manuscript:** Nilay Şengül Samancı.

## REFERENCES

1. Falagas ME, Kasiakou SK. Colistin: the revival of polymyxins for the management of multidrug-resistant gram-negative bacterial infections. *Clin Infect Dis* 2005;40(9):1333-41.
2. Yahav D, Farbman L, Leibovici L, Paul M. Colistin: new lessons on an old antibiotic. *Clin Microbiol Infect* 2012;18(1):18-29.
3. Lim LM, Ly N, Anderson D, Yang JC, Macander L, Jarkowski A 3rd, et al. Resurgence of colistin: a review of resistance, toxicity, pharmacodynamics, and dosing. *Pharmacotherapy* 2010;30(12):1279-91.
4. Garonzik SM, Li J, Thamlikitkul V, Paterson DL, Shoham S, Jacob J, et al. Population pharmacokinetics of colistin methanesulfonate and formed colistin in critically ill patients from a multicenter study provide dosing suggestions for various categories of patients. *Antimicrob Agents Chemother* 2011;55(7):3284-94.
5. Falagas ME, Rizos M, Bliziotis IA, Rellos K, Kasiakou SK, Michalopoulos A. Toxicity after prolonged (more than four weeks) administration of intravenous colistin. *BMC Infect Dis* 2005;5:1.
6. Falagas ME, Kasiakou SK. Toxicity of polymyxins: a systematic review of the evidence from old and recent studies. *Crit Care* 2006;10(1):R27.
7. Grill MF, Maganti RK. Neurotoxic effects associated with antibiotic use: management considerations. *Br J Clin Pharmacol* 2011;72(3):381-93.
8. Honore PM, Jacobs R, Lochy S, De Waele E, Van Gorp V, De Regt J, et al. Acute respiratory muscle weakness and apnea in a critically ill patient induced by colistin neurotoxicity: key potential role of hemoadsorption elimination during continuous venovenous hemofiltration. *Int J Nephrol Renovasc Dis* 2013;6:107-11.
9. Liu Y, Dai C, Gao R, Li J. Ascorbic acid protects against colistin sulfate-induced neurotoxicity in PC12 cells. *Toxicol Mech Methods* 2013;23(8):584-90.
10. Mülazımoğlu L. [The pharmacokinetics-pharmacodynamics of colistimethate sodium and colistin]. *ANKEM Derg* 2012;26(Ek 2):19-21.