Short Communication

The risk factors of colistin methanesulfonate associated nephrotoxicity

Elif Tükenmez Tigen, E. Nursen Koltka[1], Arzu Dogru[2], Melek Gura[1], Haluk Vahabaoglu[2]

Abstract

Purpose: The risk factors of colistin methanesulfonate (CMS) associated nephrotoxicity are important. Our study attempts look into the prevalence of CMS-associated nephrotoxicity in Intensive Care Units (ICUs), and related risk factors. **Materials and Methods:** The study was conducted between September 2010 and April 2012 on 55 patients who underwent CMS treatment. Nephrotoxicity risk was defined based on the Risk Injury Failure Loss End-stage kidney disease criteria. **Results:** Fifty-five patients included in the study. A total of 22 (40%) patients developed nephrotoxicity. The correlation was detected between nephrotoxicity and patients over 65 with a high Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II score. APACHE II score was revealed an independent risk factor for nephrotoxicity. **Conclusion:** Advanced age and a high APACHE II score are significant risk factors in the development of nephrotoxicity at ICUs following CMS use. Patient selection and close monitoring are critical when starting CMS treatment.

Keywords: Colistin methanesulfonate, nephrotoxicity, risk factors

Access this article online

Website: www.ijccm.org

DOI: 10.4103/0972-5229.183905

Quick Response Code:

Introduction

The use of polymyxin antibiotics dates back to the 1950s. In the ensuing years, the use was abandoned due to severe side effects such as neurotoxicity and nephrotoxicity. In recent years, questions are being raised regarding colistin methanesulfonate (CMS)-associated nephrotoxicity as CMS is back in use again for treatment of multiresistant *Acinetobacter* spp. and *Pseudomonas* spp. related infections. Some studies[1] demonstrated that CMS was not as nephrotoxic as it was feared at the outset, while some other studies[2] detected high nephrotoxicity rates. Dose of CMS, treatment duration, patient's age, and simultaneous use of vancomycin have been identified as independent risk factors in the development of nephrotoxicity.[3] This study seeks to demonstrate CMS-associated nephrotoxicity occurrences and risk factors.

Materials and Methods

The study was conducted between September 2010 and April 2012 on 55 patients over the age of 18, who underwent CMS treatment for over 72 h at a 16-bed Intensive Care Unit (ICU) in a 750-bed tertiary hospital. Nephrotoxicity risk was defined based on the Risk Injury Failure Loss End-stage (RIFLE) criteria. Evaluations included demographic data (age, sex, weight), the number of days at ICU (Acute Physiologic Assessment and Chronic Health Evaluation [APACHE] II score, urea, creatine), RIFLE score,[4] and duration of ICU hospitalization before starting on CMS. Antibiotics and other likely nephrotoxic drugs used along with CMS were noted down. Throughout CMS use, urea, creatine, creatine clearance, APACHE II, and RIFLE scores were

From:
Department of Infectious Disease, School of Medicine, Marmara University, Departments of [1]Anesthesiology and [2]Infectious Disease, Istanbul Medeniyet University Göztepe Training and Research Hospital, Istanbul, Turkey

Correspondence:
Dr. Elif Tükenmez Tigen, Marmara University School of Medicine Ustkaynarca/ Pendik, Maltepe, Istanbul, Turkey.
E-mail: fetukenmez@yahoo.com

How to cite this article: Tigen ET, Koltka EN, Dogru A, Gura M, Vahabaoglu H. The risk factors of colistin methanesulfonate associated nephrotoxicity. Indian J Crit Care Med 2016;20:353-6.

evaluated together, and they were recorded separately on the 3rd, 6th, and 9th days at the start of treatment. CMS was administered as colymicine (Koçak Pharma) at 5 mg/kg/day, 2.5–3.8 mg/kg/day, 2.5 mg/kg/day for glomerular filtration rates of > 80, 50–79, 30–49 ml/min, respectively. Patients who are receiving renal replacement treatment (RRT) were not included in the study. It is established that nephrotoxicity begins to develop onward of detecting risk (R) based on RIFLE criteria.

Statistical analysis

Statistical analyses were done using the Stata 12.1 (StataCorp, Texas, USA) program. Binary comparisons were performed using Chi-square or Fisher's test for categorical variables, two-sample-*t*-test for constant variables with normal distribution, and Wilcoxon rank-sum test for those without normal distribution.

Multivariate analyses were carried out by using the logistic regression analysis. Initial model comprised variables that were clinically significant and/or that had a $P < 0.10$ in univariate analyses. Variables were examined for parallelism and interaction. Ultimate model was obtained through the successive elimination of the insignificant variables or those of which elimination did not weaken the model.

Results

All of the 55 patients in the study received CMS i.v. treatment; 46 due to growth of multidrug-resistant (MDR) *Acinetobacter* spp., 4 due to the growth of *Pseudomonas* spp., and 5 empirically. Following diagnoses were made in the patients: Ventilator-associated pneumonia (VAP) (microbiologically documented) in 46, suspected VAP in 5, central nervous system infection in 2, soft tissue in 1, and urinary system tract infection in 1.

Table 1 shows the demographics of the 37 male and 18 female patients that were studied. Of those, 19 were over the age of 65 with a median APACHE II score of 18. Based on the RIFLE criteria, a total of 22 (40%) patients developed nephrotoxicity.

Regarding comparison of patients who did or did not develop nephrotoxicity based on the univariate analysis, it was interesting to note that nephrotoxicity developed in patients over 65 with a high APACHE II score [Table 2].

In a comparison of both groups, when the APACHE II score was <17, there was a higher number of patients with a RIFLE score of 1–3.

Table 1: Characteristics of patients

Characteristic	All patients (*n*=55)
Age, median	51.0
Age >65 (%)	19 (35)
Male (%)	37 (67)
BMI, mean (SD)	25.7 (4.5)
ICU hospitalization days, median	41.0
Hospitalization days before colistin, median	18.0
Kreatinin, median	0.7
APACHE II, median	18.0
Mechanical ventilation days	30
Duration of CMS treatment, days	11
Total CMS dosage (mg)	3600
Usage of nephrotoxic drug (%)	31 (56)

SD: Standard deviation; BMI: Body mass index; ICU: Intensive Care Unit; APACHE II: Acute Physiology and Chronic Health Evaluation-II; CMS: Colistin methanesulfonate

Table 2: The distubitions of patients developing and undeveloping nephrotoxicity

Characteristic	Patients without nephrotoxicity (*n*=33)	Patients with nephrotoxicity (*n*=22)	*P*
Age, median (IQR)	41.0 (35.0, 60.0)	72.0 (44.0, 76.0)	0.043
Age >65	7 (21%)	12 (55%)	0.011
Male	24 (73%)	13 (59%)	0.29
BMI, mean (SD)	25.3 (4.8)	26.3 (4.2)	0.39
ICU hospitalization days, median (IQR)	43.0 (25.0, 54.0)	38.0 (31.0, 49.0)	0.81
Hospitalization days before colistin, median (IQR)	16.0 (7.0, 28.0)	20.5 (13.0, 26.0)	0.27
Kreatinin, median (IQR)	0.7 (0.5, 0.8)	0.8 (0.6, 1.2)	0.20
APACHE II, median (IQR)	17.0 (14.0, 20.0)	22.0 (18.0, 28.0)	0.007
Mechanical ventilation day (IQR)	26 (16, 43)	31 (25, 47)	0.22
Duration of CMS treatment, days (IQR)	10 (8, 18)	12 (8, 15)	0.98
Total CMS dosage (mg) (IQR)	3840 (2400, 5200)	3600 (2910, 6000)	0.92
Usage of nephrotoxic drug (%)	19 (58)	12 (55)	0.82

SD: Standard deviation; BMI: Body mass index; ICU: Intensive Care Unit; CMS: Colistin methanesulfonate; IQR: Interquartile range

Multivariate analysis showed that the APACHE II score, which is calculated only when the patient arrives at the ICU, poses a nephrotoxicity risk as an independent variable [Table 3]. Of the 22 patients who developed nephrotoxicity; Injury (I), Risk (R), and Failure (F) developed in 10, 7, and 5, respectively [Table 4]. In the study, nephrotoxicity began to develop in 11 and 6 patients on the sixth and ninth days respectively after colistin treatment was started [Table 5].

None of the patients required RRT during the study.

Discussion

CMS is removed from the body through glomerular filtration. Nephrotoxicity develops with acute tubular necrosis. There are various scores available for evaluation of nephrotoxicity (i.e., RIFLE, acute kidney injury network). RIFLE is a highly specific classification due to its sensitivity in detecting acute renal impairment.

Table 3: The distrubitions of variables according to the multivariate analysis

Factors	Coefficient	95% CI	*P*
Age	0.22	−0.11-0.54	0.191
Kreatinin	0.60	−0.54-1.74	0.300
APACHE II	1.34	0.25-2.44	0.016
_cons	−0.49	−1.11-0.12	0.118

APACHE II: Acute Physiology and Chronic Health Evaluation II; CI: Confidence interval

Table 4: Distrubitions of patients according to the Risk Injury Failure Loss End-stage criterias

RIFLE	Patient *n* (%)
Risk	7 (31)
Injury	10 (45)
Failure	5 (22)
L (loss)	0 (0)
E (ESKD)	0 (0)
Total	22 (100)

RIFLE: Risk Injury Failure Loss End-stage; ESKD: End-stage kidney disease

Table 5: The distrubitions of patients number according to the development time of nephrotoxici

RIFLE (days)	Patient *n* (%)
3	1 (4.5)
6	11 (50)
9	6 (27)
12	1 (4.5)
18	1 (4.5)
21	2 (9)
Total	22 (100)

RIFLE: Risk Injury Failure Loss End-stage

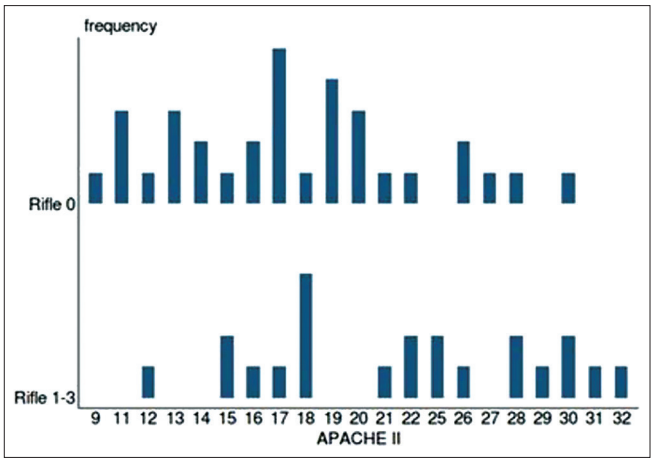

Figure 1: The distrubition of Acute Physiologic Assessment and Chronic Health Evaluation II score according to the Risk Injury Failure Loss End-stage criteria

Two recent studies using the RIFLE criteria achieved detecting mild renal impairment to the degree of 43%.[2] In the study, we evaluated nephrotoxicity according to RIFLE criteria as well. We have determined advanced age (>65) and a high APACHE II score to be significant risk factors in development of nephrotoxicity [Figure 1]. A study by Balkan *et al*. similarly points to advanced age (>60) and OR = 5.19 as a considerable risk factor in development of nephrotoxicity.[5]

In parallel with our results, a Rocco *et al*. study determined the Simplified Acute Physiology Score to be notably high in the group that developed nephrotoxicity.[6] However, some other studies demonstrated that APACHE II scored does not have an effect on development of nephrotoxicity.[7] A study conducted in Thailand identified advanced age, long-term and high dose of CMS treatment, along with simultaneous use of vancomycin, as independent risk factors in development of nephrotoxicity.[3] Another similar study emphasized CMS dose and duration to be significant with regard to nephrotoxicity.[8] Nevertheless, our study did not detect a meaningful effect created on toxicity due to CMS dose, treatment duration and simultaneous use of nephrotoxic drugs. This may be so because of the low number of cases we had.

The results of our study are analogous with recent studies that link secondary renal impairment to CMS use in critical patient groups.[3,9] Nephrotoxicity is proven to be greater with high-dose of CMS treatment. Paul *et al*. demonstrated in their study, the link between colistin treatment and crude mortality rate.[10]

Other studies point out that even though colistin use accompanied with potentially nephrotoxic drugs (i.e., intravenous radiocontrast agents, anti-inflammatory drugs, aminoglycosides, and vancomycin) increases toxicity; this is statistically insignificant.[2] Our study did not establish a meaningful relationship when used in combination with potentially toxic drugs.

Studies reveal that postcolistin AKI is dose-dependent and appears around 13.5 days (8–37 days) after starting colistin treatment.[2] Whereas, in our study, nephrotoxicity began to appear on the 6th and 9th days of treatment in 50% and 27% of the patients respectively. The study has limitations. First, it covers a small number of the population. Second, it was not designed to analyze nephrotoxicity of colistin by creating comparison in a control group. Therefore, further study with more cases is warranted.

In conclusion, colistin-associated nephrotoxicity is high in ICUs based on the RIFLE criteria. A link has been established between advanced age and high APACHE II score in development of toxicity. Therefore, this patient group must be monitored and treated closely. Today, colistin use is becoming more prevalent with increasing number of MDR-pathogen related infections.

Consequently, more in-depth studies are needed in monitoring and treatment of nephrotoxicity.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Price DJ, Graham DI. Effects of large doses of colistin sulphomethate sodium on renal function. Br Med J 1970;4:525-7.
2. Hartzell JD, Neff R, Ake J, Howard R, Olson S, Paolino K, *et al.* Nephrotoxicity associated with intravenous colistin (colistimethate sodium) treatment at a tertiary care medical center. Clin Infect Dis 2009;48:1724-8.
3. Rattanaumpawan P, Ungprasert P, Thamlikitkul V. Risk factors for colistin-associated nephrotoxicity. J Infect 2011;62:187-90.
4. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P; Acute Dialysis Quality Initiative workgroup. Acute renal failure – Definition, outcome measures, animal models, fluid therapy and information technology needs: The Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004;8:R204-12.
5. Balkan II, Dogan M, Durdu B, Batirel A, Hakyemez IN, Cetin B, *et al.* Colistin nephrotoxicity increases with age. Scand J Infect Dis 2014;46:678-85.
6. Rocco M, Montini L, Alessandri E, Venditti M, Laderchi A, De Pascale G, *et al.* Risk factors for acute kidney injury in critically ill patients receiving high intravenous doses of colistin methanesulfonate and/or other nephrotoxic antibiotics: A retrospective cohort study. Crit Care 2013;17:R174.
7. Sorlí L, Luque S, Grau S, Berenguer N, Segura C, Montero MM, *et al.* Trough colistin plasma level is an independent risk factor for nephrotoxicity: A prospective observational cohort study. BMC Infect Dis 2013;13:380.
8. Deryke CA, Crawford AJ, Uddin N, Wallace MR. Colistin dosing and nephrotoxicity in a large community teaching hospital. Antimicrob Agents Chemother 2010;54:4503-5.
9. 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.
10. Paul M, Bishara J, Levcovich A, Chowers M, Goldberg E, Singer P, *et al.* Effectiveness and safety of colistin: Prospective comparative cohort study. J Antimicrob Chemother 2010;65:1019-27.