BRIEF COMMUNICATION

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Evaluation of Risk Factors for Intravenous Colistin Use-related Nephrotoxicity

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ABSTRACT

Objectives: We investigated the incidence of and risk factors for nephrotoxicity in patients using intravenous colistin. ***Methods***: This retrospective, observational study was conducted at Karadeniz Technical University, Faculty of Medicine, clinics and intensive care unit between 1 January 2009 and 1 January 2013. Intravenous colistin was administered to 133 patients at a dose of 2.5–5.0 mg/kg/day. ***Results:*** The patients mean age was 54.3±19.1 years and the mean duration of treatment was 13.5±3.6 days. Nephrotoxicity developed in 5.0±2.8 days in 38 (28.6%) patients. Based on RIFLE (risk, injury, failure, loss of kidney function, and end-stage kidney disease) criteria, 15 (39.5%) patients were class 1, 17 (44.7%) were class 2, six (15.8%) were class 3, and none were class 4. The mean duration of development of nephrotoxicity was 5.0±2.8 days. Hemodialysis requirement was observed in two (5.2%) of the 38 patients who developed nephrotoxicity. In these cases, colistin therapy was not discontinued. Nephrotoxicity was correlated with advanced age, high pretreatment serum creatinine levels, diabetes mellitus, and chronic obstructive pulmonary disease. ***Conclusions:*** The use of colistin is relatively safe for patients that have normal renal functions. However, better standardization of the definition of nephrotoxicity in those patients with the use of scoring systems and close monitoring are necessary.

Colistin is an old polypeptide antibiotic that fell out of use but has since reappeared because of the increase in multidrug-resistant gram-negative bacteria. Originally, the nephro- and neurotoxic effects of colistin led to concerns regarding its clinical use.[1–3] We investigated the incidence of and risk factors for nephrotoxicity in patients using intravenous (IV) colistin.

METHODS

This retrospective, non-interventional, observational study assessed and monitored patients given colistin for the treatment of nosocomial infections. The study was conducted at the Karadeniz Technical University, Faculty of Medicine, clinics and intensive care unit between 1 January 2009 and 1 January 2013. The study was performed in accordance with the Helsinki Declaration, and with the approval of the hospital ethical committee. Adult patients aged 18 or over, receiving IV colistin therapy for more than 48 hours were included in the study. Diagnosis of nosocomial infections was based on US Centers for Disease Control and Prevention criteria. Patients' demographic characteristics, medical histories, underlying diseases, use of invasive equipment, side-effects associated with colistin, use of any other nephrotoxic agents together with colistin, microorganism agents in nosocomial infections, and other data such as treatment outcomes were obtained from medical records. Patients aged under 18 with acute or chronic renal impairment or receiving colistin therapy for less than 48 hours were excluded.

Only the first therapy was included in the analysis for patients who received more than one course of colistin. Colistimethate sodium was administered as recommended in the literature in three equal doses of 5 mg/kg per day, 12 hours after a single 5 mg/kg loading dose.[4] Colistin was not administered as monotherapy in any nosocomial infection, but was used in combination with a second agent such as rifampicin, imipenem, or sulbactam for 14 to 21 days. Colistin therapy was not administered empirically in any case but was started on the basis of culture antibiogram results or added to the antibiotic the patient was already taking.

The patients receiving treatment were monitored daily, both clinically and through laboratory values to look for colistin-related side-effects, particularly

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nephrotoxicity. Patients' fluid monitoring, serum urea, creatinine values and clearance (in cases of suspected renal toxicity) were monitored daily. The severity of renal injury in these cases was defined according to RIFLE (risk, injury, failure, loss of kidney function, and end-stage kidney disease) criteria. Accordingly, a rise in creatinine > 1.5 times above the normal range was defined as risk of renal failure, a rise > 2-fold was defined as renal injury, a > 3-fold increase was defined as renal failure and persistent acute renal failure. Function loss for > 4 weeks was assessed as loss.[2] The decision to continue or adjust the dosage of colistin therapy was made according to severity of the renal injury. Patients with a creatinine clearance > 80 received 2.5–5.0 mg/kg per day, 51–80 received 2.5–3.8 mg/kg per day, and 10–50 received 1.5 mg/kg per day in two to four equal doses.[4] Colistin dose was adjusted based on creatinine clearance measurements in patients with suspected nephrotoxicity, and later increased when nephrotoxicity findings improved following therapy. Factors such as use of other drugs that might cause nephrotoxicity in addition to colistin therapy and radio-opaque material intake were also investigated in these patients.

The descriptive statistical analysis was performed for all the studied variables. The data obtained in measurements of the normal distribution were analyzed using the Kolmogorov–Smirnov test (K–S test). Data in conformity with normal distribution were analyzed using Students *t*-test, and those not conforming to normal distribution using the Mann Whitney *U*-test. Data obtained by measurements are given as mean ± standard deviation (SD) and those obtained by counting as numbers and percentage. Analyses were performed using the chi-square test. The results of the analysis are presented as *p*-values, $p < 0.050$ was regarded as statistically significant.

RESULTS

The IV colistin was administered to 133 patients, 93 (69.9%) male and 40 (30.1%) female. The mean age of patients was 54.3±19.1 (range = 18–91) years. Two-thirds of patients received colistin therapy due to pneumonia, the others due to diagnoses of bacteremia, surgical site infection, and urinary tract infection or meningitis. *Acinetobacteria* were the agent in majority of the cases. Colistin was given in combination with another antibiotics in all cases. The mean length of colistin therapy was 13.5±3.6 (range = 6–21) days. Fifteen (39.5%) patients were class 1 on the basis of RIFLE criteria, 17 (44.7%) were class 2, six (15.8%) patients were class 3 and no patients were class 4.

The mean duration of development of nephrotoxicity was 5.0±2.8 days. In cases developing nephrotoxicity, the mean number of days it took for serum creatinine levels return to normal was 7.9±3.9 days after the end of the treatment. A return to normal levels was observed after treatment in all patients. The need for hemodialysis was observed in only two (5.2%) of the 38 cases developing nephrotoxicity, and colistin therapy was not discontinued due to nephrotoxicity in any case. Advanced age, high serum creatinine levels before treatment, diabetes mellitus (DM), and chronic obstructive pulmonary disease (COPD) were identified as factors associated with risk of nephrotoxicity. Radio-opaque material, other antibiotics used together, and anti-inflammatory drug use did not affect development of nephrotoxicity. Nephrotoxicity attributed to colistin was reversible in all our patients. The creatinine values returned to basal levels when treatment concluded. Crude mortality rates were similar between the nephrotoxicity and non-nephrotoxicity groups. Hemodialysis requirement occurred in only two of the patients developing nephrotoxicity, and both these patients died. Patients' demographic and clinical characteristics are summarized in Table 1.

DISCUSSION

Polymyxins first entered into clinical use in the 1950s but were not used for a long time because of their potential side effects, particularly nephrotoxicity. The increase in multidrug resistance (MDR) in gram-negative bacteria, especially *Acinetobacter*, meant that years later polymyxins again became sought after drugs for the treatment of difficult cases.[1–6]

The nephrotoxicity and neurotoxicity are the main problems encountered in the clinical use of polymyxins.[2] Nephrotoxicity frequently appears within the first few days of treatment. Inconsistent data for the incidence of nephrotoxicity have been reported in studies from 18% to 61%.[7–10] These variations have been attributed to different patient populations in studies, and differences in definitions of nephrotoxicity.[2] Efforts have been made in recent years to obtain more standardized data for

Table 1: Comparison of the demographic characteristics, underlying diseases, drug use, and prognosis of patients who did and did not develop nephrotoxicity.

Characteristics	Developed nephrotoxicity, n (%)	No nephrotoxicity, n (%)	*p*-value
Total	38 (28.6)	95 (71.4)	
Age, years, mean±SD	62.2±17.7	51.2±18.9	0.002
Gender (Male/Female)	27/11	66/29	0.858
Underlying disease			
DM	15 (39.5)	13 (13.7)	0.002
COPD	10 (26.3)	6 (6.3)	0.003
Malignancy	7 (18.4)	15 (15.8)	0.912
Trauma	10 (26.3)	36 (37.9)	0.286
Cerebrovascular disease	18 (47.4)	33 (34.7)	0.248
Abdominal surgery	6 (15.8)	18 (18.9)	0.859
Pre-treatment serum creatinine, mg dL, mean±SD	0.75±0.26	0.33±0.18	<0.001
Radio-opaque material use	21 (55.3)	48 (50.5)	0.763
Concomitant antibiotic use	38 (100.0)	93 (97.9)	0.910
Steroid use	24 (63.2)	60 (63.2)	1.000
Anti-inflammatory drug use	21 (55.3)	55 (57.9)	0.934
Hospitalization in the intensive care unit	29 (76.3)	80 (84.2)	0.412
Presence of invasive procedure	32 (84.2)	85 (89.5)	0.584
Presence of intubation	28 (73.7)	79 (83.2)	0.316
Duration of colistin, days, mean±SD	13.5±4.0	13.5±3.4	0.831
Mortality	19 (50.0)	34 (35.8)	0.188

DM: diabetes mellitus; COPD: chronic obstructive pulmonary disease.

nephrotoxicity. The RIFLE criteria are one of the most widely accepted of these.[5,11] RIFLE criteria were used in the definition of nephrotoxicity in this study for the purpose of standardization.

Studies concerning nephrotoxicity in the literature indicate very diverse risk factors such as gender and concomitant use of nephrotoxic drugs.[2,11–19] Elevation in pretreatment creatinine levels represented a risk factor for nephrotoxicity in this study. Nephrotoxicity was also more common in patients of advanced age or with DM or COPD. It has been reported in the literature that radio-opaque material used together with colistin and some other agents (such as antibiotics) can increase renal function, but no such side-effect was observed in our study.[2] Factors such as the dosage of colistin used in treatment, treatment length, and interval of use are known nephrotoxicity factors associated with mode of use.[2,20,21] However, colistin was given to all of our patients with standard posology.

Studies have reported that colistin nephrotoxicity is generally reversible, and improves following therapy dose modification or stoppage.[2,5] No hemodialysis requirement develops in the majority of patients, although it is a negative prognostic risk factor in those cases in which it does occur.[2,5] Nephrotoxicity attributed to colistin was reversible in all our patients. Patients' creatinine levels returned to basal levels at the end of therapy. Hemodialysis requirement occurred in only two patients developing nephrotoxicity, and both these patients died. On the other hand, nephrotoxicity was not assessed as a risk factor for mortality in this study.

CONCLUSION

Combined used of colistin at a dose of 2.5–5.0 mg/kg per day, three times a day after a 5 mg/kg loading dose with a second antibiotic such as rifampicin, imipenem, and sulbactam in the treatment of MDR gram-negative infections shows that colistin is relatively safe for patients that have normal basal renal functions. In addition, better standardization of the definition of nephrotoxicity in this patient group with the use of risk scoring systems such as RIFLE and close monitoring are necessary.

Disclosure
The authors declared no conflict of interest. No funding was received for this work.

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