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Colistin Dosing and Nephrotoxicity in a Large Community Teaching Hospital▽

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Thirty adult patients who received intravenous colistin (5.1 ± 2.4 mg/kg/day) were reviewed to evaluate dosing with respect to nephrotoxicity, which occurred in 10 (33%) patients within the first 5 days of treatment. Excessive colistin dosing was frequent (47%), often (71%) resulted from the use of actual body weight in obese patients, and was associated with higher rates of nephrotoxicity (80% versus 30%, $P = 0.019$).

Despite over 50 years of clinical use, definitive recommendations regarding the most efficacious and least toxic way to dose colistin do not exist (13). Package insert dosing recommendations are often used, but these are inconsistent among the different available products and were derived using inaccurate pharmacokinetic data (12, 14, 16–18). Colistin use was abandoned in the 1970s due to nephrotoxicity concerns and the introduction of safer alternatives; recent studies have demonstrated lower-than-expected rates of renal impairment (4–7). The purpose of this study was to critically evaluate colistin dosing with respect to the development of nephrotoxicity at a large community teaching hospital.

A retrospective cohort study of adult patients treated with intravenous (i.v.) colistimethate sodium for injection (Paddock Laboratories, Minneapolis, MN) for 48 h or longer from 2006 to 2008 at Orlando Health was conducted. Each vial contained 150 mg of colistin base activity (CBA). Throughout this paper, the term colistin refers to colistimethate sodium for injection and dosing is expressed as CBA. Patients were excluded if on dialysis at the start of colistin treatment. The study was approved by both the Orlando Health and University of Florida Institutional Review Boards.

The following clinical data were collected for each patient: age, gender, comorbidities, Acute Physiology and Chronic Health Evaluation (APACHE) II score (10), weight and hospital ward at the time of colistin initiation, dose and duration of all colistin administered, concomitant nephrotoxic agents, and serum creatinine (S_{CR}) levels.

Colistin dosing was evaluated based on two weight-based daily milligram of colistin per kilogram of body weight regimens: actual body weight (ABW) and ideal body weight (IBW). Ideal body weight, in kilograms, was calculated as follows: 50 + 2.3 × (height in inches exceeding 5 feet) for men; 45.5 + 2.3 × (height in inches exceeding 5 feet) for women (2). Patients were considered obese if the ABW was greater than 140% of the IBW. Classification of each dosing regimen was based on a modification of the package insert as described by Evans et al. (3), in which dosing recommendations are based on creatinine clearance (CrCl) estimates (1). A daily dose was considered excessive, normal, or low-normal if it was greater than, within, or below ±0.4 mg/kg/day, respectively, of the recommended dosing range using IBW.

Nephrotoxicity was defined as at least two consecutive S_{CR} measurements with an increase of 0.5 mg/dl from baseline at least 24 h apart after two or more days of colistin therapy. The RIFLE criteria were used to evaluate the severity of acute kidney injury (9).

All statistical analyses were performed using SPSS version 14.0 for Windows (Chicago, IL). Continuous variables were analyzed using either the *t* test or the Mann-Whitney U test; categorical data were compared using either the χ^2 or Fisher's exact test when appropriate.

Thirty patients were prescribed colistin for treatment of multidrug-resistant *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* isolated primarily from respiratory (63%) or urine (20%) sources. The mean cumulative intravenous colistin dose was 2,559 ± 2,088 mg and was administered for a median of 8 (range, 3 to 24) days. Dosing of colistin based on ABW and IBW was 3.9 ± 1.2 and 5.1 ± 2.4 mg/kg/day, respectively. Subsequent analysis of dosing is listed in Table 1. Fourteen patients (47%) received an excessive colistin dose. In 10 of these cases (71%), the dose was calculated based on ABW, instead of IBW, in obese patients. Eleven patients (37%) received low-normal doses (Table 1).

Ten patients (33%) developed nephrotoxicity during colistin treatment; all had baseline S_{CR} values ≤1.4 mg/dl, received greater than 4 mg/kg/day, and developed renal impairment within the first 5 days of treatment. The median S_{CR} at the beginning and end of therapy was 1.0 and 2.5 mg/dl, respectively. Based on RIFLE criteria, 3, 5, and 2 patients met the criteria for injury, failure, and end-stage kidney disease, respectively. Table 2 lists a comparison of patient characteristics based on development of nephrotoxicity. Patients who developed nephrotoxicity were older, had a higher baseline APACHE II score, and were more likely to have been treated in an intensive care unit

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TABLE 1. Intravenous colistin dosing based on renal function

Dose description	Recommended dosing[b] based on baseline creatinine clearance:	
	>80 ml/min (n = 20)	30–80 ml/min (n = 10)
Recommended dose[a]	5 mg/kg/day	2.5–3.8 mg/kg/day
Dosing based on:		
Actual body weight	4.2 ± 1.2	3.3 ± 1.1
Ideal body weight	5.3 ± 2.9	4.7 ± 1.2
Analysis of patient dose[c]:		
Excessive	9.0 ± 3.8 (n = 5)	5.0 ± 0.6 (n = 9)
Normal	5.0 ± 0.3 (n = 5)	None
Low-normal[c]	3.6 ± 0.7 (n = 10)	1.8 (n = 1)

[a] Dosing recommendations based on those of Evans et al. (3).
[b] All dosing expressed as mean ± standard deviation in mg/kg/day.
[c] Excessive, normal, or low-normal dosing corresponded to a daily dose that was greater than, within, or lower than 0.4 mg/kg/day, respectively, of the recommended dose using ideal body weight. Creatinine clearance as calculated by Cockcroft and Gault (1).

(ICU); however, only age was statistically significant. No differences in treatment duration or cumulative dose of colistin were observed; however, patients administered excessive daily colistin doses were significantly more likely to develop nephrotoxicity than those who received normal or low-normal doses (P = 0.019). Patients who received excessive doses because ABW was used for dose calculation in the obese were 13.2 times more likely to develop nephrotoxicity (95% confidence interval, 2.1, 82.1) than patients who received normal or low-normal doses (P = 0.005). Alternative explanations for developing nephrotoxicity that were statistically significant included receipt of concomitant diuretics and/or vasopressors. All four patients receiving vasopressors in this study developed nephrotoxicity; the remaining six patients who developed nephrotoxicity all received excessive daily colistin doses.

The major findings of this study were the 33% nephrotoxicity rate among hospitalized patients who received colistin, the statistically significant association between development of nephrotoxicity and excessive colistin dosing, and the observation that excessive colistin doses were usually administered because ABW rather than IBW was used to calculate the daily mg/kg dose. For example, in one 166-kg patient with a CrCl >120 ml/min at baseline, a 5.1-mg/kg/day dose based on ABW was given. Based on IBW, however, the dose given was 14.3 mg/kg/day. The patient developed nephrotoxicity on day 2 of therapy. Although the IBW is recommended in the package insert, data validating this recommendation do not exist and it is unclear which weight measure is most appropriate. Alternative reasons other than colistin dosing that could have explained development of nephrotoxicity were older age, receipt of diuretics, and receipt of vasopressors. After patients who received vasopressors were excluded from the analysis, nephrotoxicity was observed only in patients who received excessive daily dosing. Due to the small number of patients remaining

TABLE 2. Patient characteristics based on the development of nephrotoxicity during intravenous colistin therapy (n = 30)

Characteristic[a]	Result for patient type		P value
	Nephrotoxic (n = 10)	Nonnephrotoxic (n = 20)	
Demographics			
Age in years (mean ± SD)	57.5 ± 15.5	43.3 ± 16.5	0.033
APACHE II score	13 (7–18)	7 (3–15)	0.122
Male (%)	60	65	1.000
ICU stay during colistin administration (%)	50	25	0.231
Colistin dosing			
S_{CR} at beginning, mg/dl	1.0 (0.6–1.2)	0.8 (0.5–0.9)	0.298
S_{CR} at end, mg/dl	2.5 (2.1–4.0)	0.7 (0.5–0.9)	<0.001
CrCl at beginning, ml/min	86 (60–144)	122 (77–144)	0.301
Treatment duration, days	7 (5–16)	9 (5–12)	0.947
Every-12-h dosing frequency[b] (%)	90	65	0.210
Dose per ABW, mg/kg/day	4.2 (3.4–5.0)	4.0 (2.7–4.6)	0.301
Dose per IBW, mg/kg/day	5.5 (4.6–7.7)	4.4 (3.1–5.3)	0.011
Cumulative i.v. dose, mg	1,838 (1,519–4,613)	1,823 (975–3,184)	0.455
Cumulative i.v. + aerosolized dose, mg	1,838 (1,519–6,263)	1,823 (975–3,430)	0.455
Excessive daily dosing (all) (%)	80	30	0.019
Excessive daily dosing (because ABW used in obese patient) (%)	70	15	0.005
Alternative explanations for nephrotoxicity[c]			
i.v. contrast use (%)	20	35	0.675
Concomitant vancomycin (%)	50	30	0.425
Concomitant aminoglycosides (%)	30	40	0.702
Concomitant ACE/ARBs (%)	40	15	0.181
Concomitant diuretic use (%)	80	20	0.004
Concomitant vasopressors (%)	40	0	0.008

[a] All data represent median results (25th to 75th percentile interquartile range [IQR]) unless otherwise stated. Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit; S_{CR}, serum creatinine; CrCl, creatinine clearance as calculated by Cockcroft and Gault (1); ABW, actual body weight; IBW, ideal body weight; ACE, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; SD, standard deviation.
[b] Every-8-h and every-6-h dosing frequencies were administered in six patients and one patient, respectively. No patients received an every-24-h dosing regimen.
[c] Nonsteroidal antiinflammatory drugs, cyclooxygenase-2 inhibitors, and amphotericin B were not given in this cohort.

($n = 26$), a multivariate logistic regression model could not be performed.

The 33% rate of nephrotoxicity observed is similar to a report by Levin et al. (11) but higher than those found in other contemporary studies (4–7, 15). The majority of these studies used less than 3 mg/kg/day of CBA (4–7). The higher dosing of 5.5 mg/kg/day in patients who developed nephrotoxicity in this cohort may account for the differences among studies. Wallace et al. found a higher incidence of renal lesions in rats receiving once-daily administration of a clinically relevant colistin dose compared to a twice-daily regimen (19). Since all patients were dosed multiple times daily in this cohort, this relationship could not be evaluated. Additionally, a study by Hartzell et al. (8) found that patients treated with colistin for greater than 14 days were 3.7 times more likely to develop nephrotoxicity. Since all patients developed nephrotoxicity by day 5 of therapy, this relationship could not be evaluated.

Contemporary, reliable colistin pharmacokinetic (PK) data show a much lower concentration-time profile than previously described (12, 14, 16, 18). For example, a report by Plachouras et al. (18) shows sub-MIC colistin concentrations during the first few days of therapy in critically ill patients. These PK data suggest that increased daily doses are warranted; however, the data from this analysis suggest that administration of any daily colistin dose greater than that currently recommended (i.e., 2.5 to 5 mg/kg/day) be done cautiously, as this may increase nephrotoxicity risk.

In conclusion, excessive daily colistin dosing led to the more frequent development of nephrotoxicity and was often due to the use of the ABW for dose calculation in obese patients. These data suggest that using a measure of lean body mass, such as IBW, to dose colistin may be less nephrotoxic. Close monitoring of renal function, specifically during the first 5 days of therapy, may identify patients in whom renal toxicity of colistin is likely to occur. Further investigation must continue to identify the optimal colistin dose from both efficacy and toxicity perspectives.

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