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Colistin treatment in carbapenem-resistant *Acinetobacter baumannii* pneumonia patients: Incidence of nephrotoxicity and outcomes

Ki Hwan Kwon[a], Jin Young Oh[b], Young-Soon Yoon[b], Yun-Jeong Jeong[b], Kyung Soo Kim[c], Sung Joon Shin[c], Jae Woo Chung[d], Hee Jin Huh[d], Seok Lae Chae[d], Seong Yeon Park[e,*]

[a] *Department of Internal Medicine, Dongguk University, Ilsan Hospital, Goyang-si, Gyeonggi-do, Republic of Korea*
[b] *Divisions of Pulmonology and Critical Care Medicine, Department of Internal Medicine, Dongguk University, Ilsan Hospital, Goyang-si, Gyeonggi-do, Republic of Korea*
[c] *Division of Nephrology, Department of Internal Medicine, Dongguk University, Ilsan Hospital, Goyang-si, Gyeonggi-do, Republic of Korea*
[d] *Department of Laboratory Medicine, Dongguk University, Ilsan Hospital, Goyang-si, Gyeonggi-do, Republic of Korea*
[e] *Division of Infectious Diseases, Department of Internal Medicine, Dongguk University, Ilsan Hospital, Goyang-si, Gyeonggi-do, Republic of Korea*

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ABSTRACT

Colistimethate sodium (CMS) is increasingly used to treat multidrug-resistant Gram-negative bacilli infections. However, the incidence of CMS-associated nephrotoxicity has not been evaluated in patients with carbapenem-resistant *Acinetobacter baumannii* (CRAB) pneumonia. This retrospective study included 120 patients with CRAB pneumonia treated with intravenous CMS for ≥72 h. The objective of the study was to determine risk factors for CMS-induced nephrotoxicity and 30-day mortality in patients with CRAB pneumonia. Of the 120 patients with CRAB pneumonia, 61 (51%) developed nephrotoxicity. Multivariate analysis showed that dose per ideal body weight (IBW) [odds ratio (OR) = 1.28, 95% confidence interval (CI) 1.01–1.62; $P = 0.04$], Charlson co-morbidity index (OR = 1.31, 95% CI 1.06–1.60; $P = 0.01$) and septic shock (OR = 3.16, 95% CI 1.32–7.60; $P = 0.01$) were associated with CMS-associated nephrotoxicity. Thirty-day mortality was 33% (39/120). Multivariate analysis showed that higher daily doses of CMS per IBW [hazard ratio (HR) = 0.81, 95% CI 0.67–0.98; $P = 0.03$] and longer duration of CMS therapy (HR = 0.86, 95% CI 0.79–0.95; $P = 0.002$) were associated with increased survival. Septic shock (HR = 3.91, 95% CI 1.95–7.83; $P < 0.001$) and corticosteroid use (HR = 3.49, 95% CI 1.67–7.28; $P = 0.001$) were associated with decreased survival in patients with CRAB pneumonia. Higher daily doses of CMS per IBW, Charlson comorbidity index and septic shock were significant risk factors for CMS-associated nephrotoxicity. However, CMS-associated nephrotoxicity does not appear to have an impact on mortality.

1. Introduction

Intravenous (i.v.) colistimethate sodium (CMS; colistin) belongs to the polymyxin group of antibiotics. First isolated in Japan in 1949, it became available for clinical use in 1959 [1]. CMS fell into disuse due to its significant nephrotoxicity. It was later used as topical therapy such as aerosol therapy in patients with cystic fibrosis or in patients requiring gastrointestinal tract decontamination. Recently, CMS has become an important antibiotic against multidrug-resistant Gram-negative bacilli such as *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and carbapenem-resistant Enterobacteriaceae. The incidence of nephrotoxicity associated with CMS therapy ranges from 10% to 50% according to recent studies [2–7]. Dose per body weight is a well-known risk factor for CMS-induced nephrotoxicity, regardless of whether it is actual body weight or ideal body weight (IBW) [2–4]. However, inhomogeneous groups of patients with variable causes of infection and microbes were used in previous studies [2–6].

Carbapenem-resistant *A. baumannii* (CRAB) is a significant pathogen causing nosocomial infections [8]. The incidence of pneumonia caused by CRAB is also increasing [8,9]. Similar to other CRAB infections, CMS is an important treatment option for CRAB pneumonia. However, only a few studies have been performed on CMS-associated nephrotoxicity exclusively in CRAB pneumonia patients [10]. Therefore, this study was performed to determine the risk factors for CMS-induced nephrotoxicity and mortality in CRAB pneumonia patients.

* Corresponding author. Tel.: +82 31 961 7140; fax: +82 31 961 8331.
E-mail address: psy99ch@hanmail.net (S.Y. Park).

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2. Methods

2.1. Study population

A retrospective cohort study was conducted at Dongguk University, Ilsan Hospital (Goyang-si, South Korea). The local Institutional Review Board approved the study. Medical records of patients who received i.v. CMS for CRAB pneumonia between May 2011 and February 2014 were reviewed. Exclusion criteria were: (i) patients who received CMS for <72 h; (ii) patients who received CMS for another infection (such as urinary tract infection, catheter-related bloodstream infection or skin and soft-tissue infection); (iii) patients who received renal replacement therapy before CMS therapy; and (iv) patients who were <18 years of age. If patients received CMS therapy repeatedly during their hospital stay, only the first episode was included in the study.

2.2. Data recording

Patients with nephrotoxicity due to CMS use were compared with patients with no nephrotoxicity after CMS use in terms of risk factors and outcomes. Nephrotoxicity was graded according to the RIFLE criteria [11]. The following variables were recorded: demographics; duration and dosage of CMS therapy; comorbidity using the Charlson comorbidity index (CCI) [12]; and severity of disease using the Acute Physiology and Chronic Health Evaluation (APACHE) II score [13]. The CCI is calculated by adding the patient's comorbidity score to their age score. Levels of serum creatinine (SCr) were checked before and at the end of CMS therapy. History of concomitant use of other nephrotoxins [vancomycin, non-steroidal anti-inflammatory drugs, angiotensin-converting enzyme (ACE) inhibitors, aldosterone receptor blockers (ARBs), loop diuretics, rifampicin, amphotericin B and radiocontrast agents] was also noted. The primary outcome was the development of nephrotoxicity during CMS treatment. Secondary outcomes were 30-day mortality and CMS-associated toxicity such as neurotoxicity, muscular weakness and respiratory adverse effects.

2.3. Definition

The definition of pneumonia is presented in Table 1 [9]. Blood cultures were obtained from patients with pneumonia before antibiotic administration. Intensive care unit (ICU)-acquired pneumonia was defined as pneumonia that occurred ≥48 h after ICU admission. Ventilator-associated pneumonia (VAP) referred to pneumonia arising ≥48 h after endotracheal intubation [9]. Baseline glomerular filtration rate (GFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation formula [14]. RIFLE criteria are defined as follows: risk (R) for increased SCr level × 1.5 or GFR decrease >25%; injury (I) for increased SCr level × 2 or GFR decrease >50%; failure (F) for increased SCr level × 3 or GFR decrease >75% or SCr level >4 mg/dL; loss (L) for persistent acute renal failure or complete loss of function for >4 weeks; and end-stage kidney diseases (E) that lasted for 3 months [11]. Chronic kidney disease (CKD) is defined as GFR < 60 mL/min/1.73 m^2 that lasted for ≥3 months [15]. Corticosteroid treatment was considered when dosage equivalent was ≥15 mg of prednisolone per day during CMS treatment [16].

Table 1
Definition of pneumonia.

(1) New or persistent pulmonary infiltrate
(2) Two or more symptoms and signs
(a) Body temperature >38.5 °C or <35.5 °C
(b) Leucocyte count >12,000/mm^3 or <4000/mm^3
(c) Purulent sputum
(3) Isolation of microbial organisms by the following methods including
(a) Quantitative culture (≥10^4 CFU/mL) of BAL specimen
(b) Semiquantitative culture (moderate or heavy growth) of bronchoscopic aspirates, BAL specimen or endotracheal aspirates with WBCs >25/HPF on Gram staining
(c) Adequate sputum with WBCs >25/HPF and epithelial cells <10 on Gram staining

BAL, bronchoalveolar lavage; WBC, white blood cell; HPF, high-power field.

2.4. Drug administration

The CMS used in this study was Coly–Mycin® M Parenteral (SteriMax Pharmaceuticals, Mississauga, ON, Canada) supplied as 400 mg of CMS (150 mg of colistin base activity) per vial. Intravenous CMS dosing at Ilsan Hospital is not protocol-driven. However, the usual frequency and renal adjustment are reflected by recommendations from the package insert. The classification of each dosing regimen was based on modification of the package insert as described by Evans et al. [5,17]. Dosing recommendations were based on creatinine clearance. Administered CMS doses were 2.5–5 mg/kg/day divided into two to four equal doses [5,17]. No patient received a loading dose of CMS. Treatment duration was determined based on the clinical response during follow-up.

2.5. Microbiological methods

Respiratory tract and blood cultures were processed using a Phoenix NMIC/ID-4 panel (BD, Sparks, MD). Results of carbapenem and colistin susceptibility testing were interpreted according to Clinical and Laboratory Standards Institute (CLSI) guidelines [18].

2.6. Statistical analysis

Continuous variables were compared using the Mann–Whitney *U*-test or Student's *t*-test as appropriate. Categorical variables were compared using Pearson χ^2 test or Fisher's exact test. Univariate and multivariate analyses of risk factors associated with CMS-induced nephrotoxicity were performed using logistic regression models. Variables that emerged from this analysis with a *P*-value of <0.1 were candidates for inclusion in the multivariate analysis. Univariate and multivariate analyses of risk factors associated with 30-day mortality were performed using Cox proportional hazards regression models. Statistical analyses were performed with IBM SPSS Statistics for Windows v.20.0 (IBM Corp., Armonk, NY). All tests were two-sided and statistical significance was considered when the *P*-value was <0.05.

3. Results

3.1. Patient characteristics

A total of 120 patients with CRAB pneumonia treated with i.v. CMS during the study period were used for the final analysis (Fig. 1). The baseline characteristics of patients are summarised in Table 2. The median age was 77 years [interquartile rage (IQR) 69–83 years]. Most patients (78; 65%) were male. Patients who developed nephrotoxicity received significantly higher doses per IBW compared with patients who did not develop nephrotoxicity. The median length of CMS therapy was 10 days (IQR 7–14 days). The median cumulative CMS dose was 2000 mg (IQR 1312–3000 mg). A total of 88 patients (73%) developed CRAB pneumonia ≥48 h after ICU admission. A total of 58 patients (48%) were diagnosed as having VAP. Twelve patients (10%) had CKD, including nine patients at stage 3 and three patients at stage 4. A total of 36 patients (30%) with CRAB pneumonia presented with septic shock. However, none of the patients developed bacteraemia. Of the 120 patients with CRAB pneumonia, 70 (58%) received CMS monotherapy. The other

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