International Journal of Infectious Diseases 35 (2015) 18–23

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

The efficacy and nephrotoxicity associated with colistin use in an intensive care unit in Vietnam: Use of colistin in a population of lower body weight

Nguyen Gia Binh [a], Kayoko Hayakawa [b,*], Dao Xuan Co [a], Nguyen Dang Tuan [a], Nguyen Hoang Anh [c], Nguyen Thi Hong Thuy [d], Doan Mai Phuong [e], Nguyen Thi Lien Huong [c], Pham Thi Phuong Thuy [f], Ngo Qui Chau [g], Pham Hong Nhung [e], Do Thi Hong Gam [d], Duong Thanh Hai [d], Tran Thu Huong [d], Le Van Anh [d], Nozomi Takeshita [b], Norio Ohmagari [b]

[a] Intensive Care Unit of Bach Mai Hospital, Hanoi, Vietnam
[b] Disease Control and Prevention Center, National Center for Global Health and Medicine, Tokyo, Japan
[c] Hanoi University of Pharmacy, Hanoi, Vietnam
[d] Pharmacy department of Bach Mai Hospital, Hanoi, Vietnam
[e] Microbiology Department of Bach Mai hospital, Hanoi, Vietnam
[f] National Center for Global Health and Medicine - Bach Mai hospital Medical Collaboration Center
[g] Respiratory Department, Bach Mai Hospital, Hanoi, Vietnam

ARTICLE INFO

Article history:
Received 11 March 2015
Received in revised form 21 March 2015
Accepted 26 March 2015

Keywords:
Colistin
Hospital acquired infection
ICU
Nephrotoxicity
Asia
Lower body weight

SUMMARY

Background: There has been a growing need for colistin as a key drug for the treatment of MDR-GNB infection. Information on colistin use in Asian population is limited.
Methods: A retrospective observational study was conducted to assess the efficacy and nephrotoxicity in critically ill adult patients who received intravenous colistin for MDR-GNB infection in the intensive care unit (ICU) at Bach Mai Hospital in Hanoi, Vietnam. Colistin was administered according to the dosing guideline that was based on pharmacokinetic, pharmacodynamic and toxicodynamic principles, adjusted by body weight and creatinine clearance.
Results: Twenty-eight eligible patients were included. The mean patient age was 60 ± 20.4 years. The mean body weight was 53 ± 8.6 kg. The mean daily dose of colistin was 4.1 ± 1.6 MIU, and the mean cumulative dose of colistin was 48.2 ± 22.8 MIU. Colistin therapies were classified as clinically effective in 19 (67.9%) cases. Six (21.4%) patients developed nephrotoxicity during the study period according to RIFLE criteria.
Conclusion: A personalized dosing protocol of colistin was effective, with low nephrotoxicity, among critically ill Vietnamese patients with low body weight. Further studies are warranted for assessing the efficacy and toxicity in a larger cohort.

1. Introduction

Multi-drug resistant gram-negative bacteria, such as MDR-*Acinetobacter baumannii*, carbapenemase-producing *Enterobacteriaceae*, MDR-*Pseudomonas aeruginosa* have spread rapidly worldwide, including Asia.[1] Colistin, which is produced *in vivo* after hydrolyzation of its prodrug colistimethate sodium, has been increasingly employed for over a decade as a key drug for the treatment of these MDR-GNB.[2] Colistin is known for its nephrotoxicity which initially resulted in abundance of its clinical use in 1970s.[2] Majority of recent studies on the clinical use of colistin were conducted in Europe or North America, and there has been debate on the appropriate dosing and its relation to the efficacy and nephrotoxicity of colistin.[2] Information on colistin use pertaining to the Asian population is limited. Recently, the interim guideline to administer colistin in critically ill patients based on pharmacokinetic, pharmacodynamic, and toxicodynamic principles

* Corresponding author. 1-21-1 Toyama, Shinjuku, Tokyo, 162-0052, Japan, Disease Control and Prevention Center, National Center for Global Health and Medicine, Tokyo, Japan. Tel.: +1 80 6871 9083.
E-mail address: kayokohayakawa@gmail.com (K. Hayakawa).

http://dx.doi.org/10.1016/j.ijid.2015.03.020

has been proposed.[3] The efficacy and toxicity of such "personalized" administration of colistin has not been well evaluated worldwide, even less so in Asian countries where people tend to have lower body weight than in Europe or North America. In this study, we evaluated the efficacy and nephrotoxicity of personalized administration of colistin in critically-ill patients admitted to ICU in Vietnam.

2. Methods

2.1. Study Design and Patient Population

This was a retrospective observational study to assess the efficacy and nephrotoxicity in critically ill patients who received intravenous colistin at Bach Mai Hospital (BMH) between August 15, 2013 and January 15 2014. BMH has 2000 beds and serves as a tertiary care hospital in Hanoi, Vietnam. The study was approved by Bach Mai Hospital institutional review board. Adult patients aged greater than 18 years were included in the study if they were admitted to the intensive care unit (ICU) and received intravenous colistin for hospital acquired infection due to MDR-GNB with positive microbiological culture. Hospital acquired infection (HAI) was determined according to CDC/NHSN definitions[4] and according to multiple physicians' evaluation. Patients were excluded if they were pregnant or breast-feeding or were receiving renal replacement therapy (intermittent hemodialysis or continuous renal replacement therapy) before the initiation of colistin. Patients were excluded if they received colistin for less than five days, to ensure adequate exposure to the drug.

2.2. Microbiology

BMH has a single centralized microbiology laboratory. Standard identification and susceptibility testing of clinical isolates were performed in accordance with the Clinical and Laboratory Standards Institute (CLSI) criteria.[5] The minimum inhibitory concentrations (MICs) of collistin were determined by E-test (Sysmex-bioMerieux, Tokyo, Japan) according to the manufacturer's instructions.

2.3. Colistin administration

The colistin product used in this study was Coly-Mycin® produced by Sanofi-Aventis. Dosing of intravenous colistin was prospectively reviewed by clinical pharmacists. The institutional guideline for colistin dosing was as follows[3]:

Loading dose (Colistin Base Activity [CBA], mg) = C-Target × 2 × Total actual body weight (kg).

Maintenance dose (CBA, mg) = C-target × (1.5 × CrCl [Creatinine clearance, mL/min] + 30).

Maintenance dose was initiated 24 hours after loading dose infusion. C-target was calculated as follows. C-target was equal to the identified colistin MIC for the causative organism of HAI. The doses calculated based on CBA (mg) were divided by 33.3 to convert them to MIU (million international units). The total daily dosage was divided into two doses for twice-daily administration.

Each bottle of colistin was dissolved in 50 mL of normal saline solution (0.9% NaCl) and was infused immediately over 30 minutes to 2 hours following its dissolution. Clinical pharmacists rechecked and recalculated the maintaining colistin dose according to the patient's measured renal function during colistin therapy. Body weights and CrCl were measured within 2 days of colistin administration. Nebulized colistin was not used throughout the study period.

2.4. Data Collection

The following parameters were retrieved from the medical records of patients in the study: age, sex, weight, underlying diseases, baseline serum creatinine concentration, Charlson's score,[6] Acute Physiology and Chronic Health Evaluation (APACHE) II score,[7] Clinical Pulmonary Infection Score (CPIS),[8] and Sequential Organ Failure Assessment (SOFA) score on ICU admission.[9] The information on the use of other nephrotoxic drugs (NSAIDs, furosemide, contrast agent, angiotensin-converting enzyme inhibitors) was also collected.

2.5. Clinical assessment

Clinical assessments were conducted at 3 time points: the first was prior to using colistin; the second was after day 5 of colistin treatment; the last point was after discontinuing colistin. Multiple physicians involved in the patients' care evaluated the clinical effectiveness of colistin therapy at each time point, based on the resolution, persistence or worsening of symptoms and signs of infection.

2.6. Microbiological assessment

Microbiological culture samples were collected at two time points, the first was prior to administering colistin and the second was after day 5 of colistin treatment. Samples were transferred to the microbiology department, and sample culture result and MICs were determined. Microbiological efficacy was evaluated based on the comparison of two consecutive culture results; i.e., if the second culture was negative, then it was evaluated as microbiologically effective.

2.7. Nephrotoxicity assessment

Daily serum creatinine level was recorded from the first day of colistin therapy until discharge or death. Nephrotoxicity was defined based on the increase in the serum creatinine concentration of $\geq$50 percent as per RIFLE (risk, injury, failure, loss, and end-stage kidney disease) criteria.[10]

2.8. Statistical Analysis

All analyses were performed using SPSS 20. Bivariate analyses were performed using the Fisher's exact test or the Chi-square test for categorical variables and the t-test or the Mann-Whitney U test for continuous variables. All P-values were two-sided, a p value of less than 0.05 was considered to indicate a statistically significant difference. Throughout the text, the percentages displayed are the "valid percent", which indicates the percent excluding the missing data from the denominator.

3. Results

During the study period, 28 eligible patients were identified. The mean age was 60 (±20.4; range: 19-88) years, and 18 (64%) were male (Table 1). The mean body weight of the study cohort was 53 (±8.6; range: 35.5-75) kg. Eight (28.6%) patients had preexisting renal failure prior to the administration of colistin, which was defined by a serum creatinine (Scr) value > 1.2 mg/dl. The majority (n = 26, 92.9%) of patients had ventilator-associated pneumonia (VAP), and 2 (7.1%) patients had blood-stream infections.

Acinetobacter baumannii were most frequently isolated (n = 24 [85.7%]; 23 from sputum, 1 from blood), followed by *Pseudomonas aeruginosa* (n = 3 [10.7%]; 3 from sputum), and *Klebsiella pneumonia* (n = 3 [10.7%]; 2 from sputum and 1 from