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Old agent, new experience: colistin use in the paediatric Intensive Care Unit—a multicentre study

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ABSTRACT

Nosocomial infections caused by multidrug-resistant (MDR) microorganisms are a common problem around the world, especially in Intensive Care Units. The aim of this study was to investigate the efficacy and safety of colistin therapy in paediatric patients with severe nosocomial infections caused by MDR Gram-negative bacteria. There were 87 episodes in 79 paediatric Intensive Care Unit patients in five different hospitals; each patient was treated intravenously with colistin and evaluated. Of the 79 patients, 54.4% were male and the median age was 30 months. The most commonly isolated microorganism was *Acinetobacter baumannii*, the most common isolation site was tracheal aspirate fluid and the most common type of infection was ventilator-associated pneumonia. The mean colistin dose in patients without renal failure was 5.4 ± 0.6 mg/kg/day, the mean therapy duration was 17.2 ± 8.4 days and the favourable outcome rate was 83.9%. Serious side effects were seen in four patient episodes (4.6%) during therapy; two patients suffered renal failure and the others had convulsive seizures. Other patients tolerated the drug well. The infection-related mortality rate was 11.5% and the probability of death within the first 9 days of treatment was 10 times higher than after the first 9 days. In conclusion, this study suggests that colistin is effective in the treatment of severe nosocomial infections caused by MDR Gram-negative bacteria and is generally well tolerated by patients, even after relatively long-term use.

1. Introduction

Multidrug resistance in Gram-negative bacteria is defined as resistance of microorganisms to at least three different groups of antibiotics with intrinsic activity against Gram-negative bacteria, such as β-lactams, aminoglycosides, quinolones and carbapenems [1]. Nosocomial infections caused by multidrug-resistant (MDR) microorganisms are common worldwide and have an increasing incidence [2,3]. Even so, no new drugs have been discovered to combat such microorganisms [4]. This situation has led to renewed interest in treatment using colistin, which has a bactericidal effect, although its clinical use has been limited due to side effects [2,5–7]. A number of studies have been conducted on the systemic use of colistin in adults, mostly in critically ill patients [7–9]. However, information on the efficacy and safety of colistin therapy in children is limited [2,6,10]. The aim of this multicentre study was to investigate the efficacy and safety of colistin therapy in the treatment of serious nosocomial infections in paediatric Intensive Care Unit (PICU) patients.

2. Materials and methods

The study was performed in the PICUs of five university hospitals situated in different geographic regions of Turkey. Paediatric

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patients treated with intravenous (i.v.) colistin for serious nosocomial infections from January 2008 to June 2011 were analysed retrospectively. Neonates and patients who received colistin treatment for <2 days were excluded. The following parameters were examined from the medical records of patients: demographic characteristics; medical histories; predisposing factors for systemic infection; presence of medical devices (e.g. central venous catheters, Foley catheters and endotracheal and tracheostomy tubes); previous and concomitant drug use (e.g. antimicrobials and sedatives or analgesic agents that can mask neurological side effects or drugs that can potentiate nephrotoxicity); types and antimicrobial susceptibilities of causative microorganisms; types of infection [e.g. haematogenous infection, ventilator-associated pneumonia (VAP), soft tissue infection]; dosage, duration, route of administration and side effects of colistin; and results of antimicrobial therapy and prognosis. Medical records for each patient were also investigated for signs of neurotoxicity (e.g. neuromuscular blockade, seizures or changes in level of consciousness) that occurred during treatment. The levels of blood urea nitrogen (BUN), creatinine, C-reactive protein (CRP) and procalcitonin as well as leukocyte and platelet counts were recorded at baseline, at the highest and lowest points of the therapy cycle and at the end of the treatment.

In all centres participating in the study, the decision to start or terminate colistin treatment was made by the PICU staff and infectious diseases consultant. A Paediatric Risk of Mortality (PRISM III) score was used to determine the severity of illness and a Pediatric Logistic Organ Dysfunction (PELOD) score was used to determine organ dysfunction. Nephrotoxicity was defined in patients with normal renal function as serum creatinine levels >1.1 mg/dL, by a >50% reduction in creatinine clearance (CL_{Cr}) or by the need for renal replacement therapy (RRT) at any time during treatment.

Nosocomial infections, catheter-related infections and VAP were defined according to the US Centers for Disease Control and Prevention (CDC) definitions [11] and diagnosis of sepsis was made according to the International Pediatric Sepsis Consensus Conference [12]. Empirical treatment was defined as application of colistin treatment on the basis of surveillance information or inadequate response of the infection to other antimicrobial agents.

The effectiveness of treatment was measured by clinical and laboratory findings and by bacteriological response. Clinical response was defined as complete recovery from clinical findings of the index infection at the end of colistin treatment. Failure of treatment was defined as the persistence or worsening of initial symptoms or the development of new infection. Microbiological response was classified according to the final culture results. Bacteriological response was defined as eradication of the causative microorganism in the final culture; an unsatisfactory bacteriological response was defined as the persistence of causative pathogens. Microbiological sensitivity results were interpreted according to current Clinical and Laboratory Standards Institute (CLSI) guidelines [13].

The primary outcomes in the study were mortality and clinical and microbiological responses. The secondary outcome was the development of side effects during colistin treatment. The study was approved by the local ethics committee of Ondokuz Mayıs University (Samsun, Turkey). Descriptive statistics were used in the data analysis.

3. Results

A total of 87 episodes of nosocomial infection in 79 PICU patients treated with i.v. colistin were evaluated. Six patients received two courses of colistin, one patient received three courses of treatment and the remaining patients received one course of treatment. All patients received the same colistimethate sodium preparation (1 mg of colistin is approximately equal to 12 500 IU) intravenously.

Table 1
Microbiological findings and demographic and clinical characteristics of 87 episodes of severe nosocomial infection caused by multidrug-resistant Gram-negative bacteria in 79 paediatric Intensive Care Unit (PICU) patients.

Characteristic	
Age (months) [median (range)]	30 (3–216)
Age <3 years old [*n* (%)]	50/79 (63.3)
Male [*n* (%)]	43/79 (54.4)
Underlying disease [*n* (%)]	62/79 (78.5)
Chronic neurological or neuromuscular disease	26
Congenital heart disease	10
Primary immune deficiency	8
Inherited metabolic disorders	7
Malignancy	2
Others (collagen tissue disease, chronic renal failure, chronic lung disease, etc.)	9
Risk factors for systemic infections [*n* (%)]	24/79 (30.4)
Primary immune deficiency	8
Immune suppressive treatment	6
Others (surgical intervention, decubitus ulcer, skin defect, etc.)	10
Length of stay in PICU before infection [median (range)]	14 (0–115)
Total length of stay in hospital before infection [median (range)]	21 (0–123)
Application of mechanical ventilation [*n* (%)]	86/87 (98.9)
Duration of mechanical ventilation (days) [median (range)]	14 (0–115)
Devices	
Tracheostomy	46/87 (52.9)
Endotracheal tube	40/87 (46.0)
Foley catheter	63/87 (72.4)
Central venous or arterial catheter	34/87 (39.1)
Haemodialysis or peritoneal dialysis catheter	3/87 (3.4)
Others (thorax tube, external ventricular drainage catheter)	2/87 (2.3)
PRISM III score (mean ± S.D.)	18.9 ± 9.2
PELOD score (mean ± S.D.)	17.2 ± 10.7
Isolated microorganism [*n* (%)]	
Acinetobacter baumannii	52/87 (59.8)
Pseudomonas aeruginosa	16/87 (18.4)
Klebsiella pneumoniae	1/87 (1.1)
A. baumannii + *P. aeruginosa* or *K. pneumoniae*	7/87 (8.0)
Site of isolated microorganism	
Tracheal aspirate fluid	63/87 (72.4)
Blood	28/87 (32.2)
Skin swabs, conjunctival swabs	5/87 (5.7)
Others (peritoneal and cerebrospinal fluid)	2/87 (2.3)

PRISM, Paediatric Risk of Mortality; S.D., standard deviation; PELOD, Pediatric Logistic Organ Dysfunction.

The drug dose was estimated based on actual body weight and CL_{Cr}. Microbiological findings and demographic and clinical characteristics of the study patients are shown in Table 1.

Colistin treatment was initiated for culture-positive infection in 67 episodes (77%) and was started empirically while taking into account surveillance information in 20 episodes (23%) owing to uncontrolled fever or progressive sepsis despite other antimicrobials. In nine of the empirically treated patients, MDR Gram-negative bacteria were isolated from cultures collected before treatment. In 22 (25.3%) of the episodes the infection was polymicrobial and there was co-infection caused by microorganisms other than MDR Gram-negative bacteria. All patients had received antimicrobial therapy prior to colistin treatment. Colistin was used in combination with other antimicrobial agents in all episodes, except for two episodes treated with colistin alone. The properties of the nosocomial infections and infections treated with colistin are shown in Table 2.

Colistin was administered intravenously to all patients. In addition, the drug was administered intraventricularly to only one patient at a dose of 10 mg/day for 21 days owing to hydrocephaly and shunt infection. The average dose of colistin in patients without renal failure was 5.4 ± 0.6 mg/kg/day. The drug doses for the