Neurotoxicity, nephrotoxicity, and severe infusion-related adverse effects in patients receiving high doses of polymyxin B

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Introduction

Polymyxins have been widely used for the treatment of extensively-drug-resistant Gram-negative bacteria. Unbound area under the concentration curve has been shown to be the pharmacokinetic/pharmacodynamic index driving antimicrobial activity of polymyxins.

Clinical studies with polymyxin B have shown that higher doses have been associated with lower mortality. Despite this, unfavorable clinical outcomes rates remain very high. In addition, resistance to these agents have been increasingly reported. In vitro studies have shown that emergence of resistance is relatively common, even in isolates exposed to polymyxins concentrations similar to those expected *in vivo* after "adequate" therapeutic regimens. To counteract this occurrence, *in vitro* exposures to very high concentrations of polymyxin B have been evaluated, with promising results. However, toxicity of such regimes is largely unknown, particularly the acute or infusion-related toxicity.

In this study, we aimed to evaluate neurotoxicity, nephrotoxicity and severe infusion-related adverse effects of high-dose polymyxin B (PMB).

Methods

A retrospective cohort study assessing patients hospitalized from January/2013 to December/2015 receiving total PMB dose ≥250mg/day or >3mg/kg/day were included. The following outcomes were assessed during therapy: neurotoxicity, acute kidney injury (AKI) according RIFLE classification, death occurring during polymuxin B infusion and during therapy. Neurotoxicity were classified according to Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 (National Institutes of Health, Bethesda, MD, USA) as mild, moderate, severe/medically significant, life-threatening, and cause of death.

Table 1. Main characteristics of cohort patients and PMB treatment.

Variable	Total (*n*=223)
Female sex	96 (43.0%)
Age, years (mean ± SD)	57 ± 17
Weight , kilograms (mean ± SD)	79 ± 25
ICU	149 (67.0%)
Charlson co-morbidity Index	
Median (IQR)	4 (2-6)
Concomitant Drugs	
Sedatives	146 (65.0%)
Neuromuscular blockers	24 (10.0%)
Vasoactive drugs	138 (61.0%)
Dialysis	96 (43.0%)
Calculated Glomerular Filtration Rate (mL/min)	
Median	86 (139-52)
PMB dose (mg/kg/day)	
Mean ± SD	3.61 ± 0.96
Loading dose (yes)	23 (10.0%)
Total daily dose (mg)	
Mean ± SD	272 ± 59
In-hospital mortality	135 (60.0%)
30-day	97(43.0%)
During treatment	57(26.0%)
During infusion	0 (0.0%)

Table 2. Patients with neurologic adverse events.

	Age	Weight	PMB dose (mg/kg/day)	Total daily dose (mg)	Neurotoxicity effects	CAE grade
CASE 1	38	71	4.2	294	Perioral paresthesia Convergent strabismus	Mild to moderate Severe
CASE 2	71	151	2.98	450	Perioral paresthesia	Mild to moderate
CASE 3	37	70	5.7	400	Paresthesia and dizziness	Mild to moderate
CASE 4	23	74	3.63	270	Perioral paresthesia, dizziness Hypoxemia	Mild to moderate Life-threatening
CASE 5	40	60	3.3	200	Thoracic pain and respiratory dysfunction	Life-threatening
CASE 6	34	57	5.6	300	Dizziness and confusion	Severe

Results

A total of 223 patients were included. Characteristics of patients are summarized in Table 1. Most common comorbidities were diabetes (n=55; 24.7%), chronic kidney disease (n=55; 24.7%) and heart failure (n=49; 22.0%). Median duration of PMB treatment was 7 days (IQR 4-12).

Six of 223 patients presented neurotoxicity during PMB therapy (all presented with the onset during PMB infusion), resulting in a crude incidence of 2.7% (95%CI= 0.58%-4.82%): one of 149 patient was in ICU (crude incidence 0.7%; 95%CI= 0%-2.0%) and five of 74 were outside ICU (crude incidence 6.8%; 95%CI 1.1%-12.5%). Some aspects of patients who developed neurotoxicity are described in Table 2. In an univariate analysis, patients with neurotoxicity tend to be younger than patients without neurotoxicity (mean age 40±16, vs. 57±16.7; p=0.15) and presented a lower median Charlson comorbidity index: 1.5 (IQR 0-2) vs. 4 (IQR 2-6); p=0.01.

For the evaluation of acute kidney injury (AKI), 127 patients were included. AKI was observed in 53 patients (42.0%): Risk= 14 (26.5%), Injury= 14 (26.5%) and Failure= 25 (47.0%).

Conclusions

- In patients receiving high-dosage regimens of PMB, incidence of neurotoxicity was low (2.7%);
- No dose-response relationship was found, in terms of neurologic adverse events;
- Incidence of neurotoxicity might be underestimated in ICU patients because patients were mostly sedated.
- Acute kidney injury rates observed were comparable to conventinal dosage regimens.