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Efficacy and Toxicity of High-Dose Colistin in Multidrug-Resistant Gram-Negative Bacilli Infections: A Comparative Study of a Matched Series

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Key Words
Colistin · Multidrug resistance · Gram-negative bacilli

Abstract
Background: Colistimethate sodium (CMS) is the commercialized form of colistin that is effective against multiresistant Gram-negative bacilli. Its main side effects are nephrotoxicity and neurotoxicity. Pharmacodynamic dosages showed that they were infratherapeutic. Therefore, strategies with higher doses were proposed. The aim of this study was to assess the efficiency and toxicity of higher-dose CMS by comparing two treatment strategies: high-dose CMS versus standard-dose CMS. ***Methods:*** A prospective and comparative study of two matched groups was conducted. Fourty-six patients in each group were matched for age, severity and nature of infection. In the high-dose colistin group, CMS was administered at a loading dose of 9 MIU followed by a maintenance dose of 4.5 MIU/12 h. In the second group, retrospectively analyzed, colistin was administered at 6 MIU/day. For each group, clinical results, bacteriological eradication and daily creatinine clearance were recorded. Primary outcome measures were clinical cure defined as disappearance of infectious signs and eradication of microorganisms in all the follow-up cultures. Secondary outcome measures were incidence of acute renal failure and mortality. ***Results:*** Ninety-two patients were analyzed by matching. There was a higher cure rate in the high-dose group (63 vs. 41.3%, p = 0.04). No higher risk of nephrotoxicity was found by increasing daily doses of colistin (32.2 versus 26%, p = 0.64). Similarly, there was no significant difference in the time to onset of renal failure (8.32 vs. 11 days, p = 1) or in the requirement of hemodialysis (26.6 vs. 41%, p = 1). ***Conclusion:*** The high-dose colistin regimen is more efficient, without significant renal or neurological toxicity.

Introduction

Colistin is the most widely used polymyxin antibiotic. It is most often administered as its prodrug colistimethate sodium (CMS). It is considered an 'old antimicrobial', and was abandoned for almost 30 years because of significant renal and neurological toxicity [1]. In the last few years, with the paucity of antibiotic options available, interest has been renewed in the old antibiotics, polymyxins, as a 'last-line' therapy in the management of infections caused by multidrug-resistant, Gram-negative bacilli (MR GNB) including *Pseudomonas*, *Acinetobacter*, *Klebsiella* and *Enterobacter* spp. [2–6].

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A similar tendency can be observed in Tunisian intensive care units (ICUs), where GNB, mainly *Acinetobacter baumanii* and *Pseudomonas aeruginosa*, are commonly incriminated in nosocomial infections and their multidrug resistance is increasing [7–9]. Susceptibility in vitro to colistin has been maintained, however, leading to the use of this drug as a salvage therapy in >90% of nosocomial infections [9].

Colistin has a concentration-dependent bactericidal activity, and its therapeutic efficacy strictly depends on the ratio of the peak level to the minimum inhibitory concentration (MIC) or the ratio of the area under the curve to the MIC [1]. In critically ill patients, current colistin dosing regimens result both in a subtherapeutic peak concentration and a prolonged time to steady state, leading to suboptimal and delayed effective treatment [1, 10, 11]. Therefore, strategies involving higher doses and longer dosing intervals along with loading doses have been proposed, in order to attain more effective killing [12–14]. However, the clinical efficacy and renal toxicity of such regimens have still to be assessed.

In our unit, the administration of colistin is set at a dose of 6 million international units (MIU) over 24 h continuously, without a loading dose. Before adopting a new strategy involving a high-dose CMS regimen, we proceeded to make an evaluation by comparing the 2 therapeutic approaches.

The purpose of this study was to test the clinical and bacteriological efficiency and toxicity of CMS at higher doses preceded by loading doses. To respond to this objective, we performed a comparison between 2 matched groups receiving CMS at a high dose with a loading dose versus CMS at a standard dose.

Materials and Methods

Design Study and Patients

This was a retro-prospective and comparative study of 2 matched series. Three matching criteria were considered: age, disease severity index or Simplified Acute Physiology Score II (SAPS II) and site of infection. The study was conducted at the Medical Resuscitation Unit, Tunisian University Hospital Center of La Rabta, over a period of 17 months (April 2013 to August 2014).

All patients who were treated with CMS for MR GNB infections were included. The exclusion criteria were treatment duration with CMS of <24 h and pregnancy. The CMS used was Colimycine® powder (Sanofi Winthrop Industry).

The patients were divided into 2 groups. The trial group or high-dose colistin group was recruited prospectively. The control group or standard-dose colistin group, had CMS prescribed according to the convention of the Resuscitation Unit before December 2013, i.e. this control group was recruited retrospectively. For improving the comparability between the groups, they were matched according to 3 criteria: age, SAPS II and infection site.

Colistin Administration

The high-dose colistin group received CMS intravenously (i.v.), with a loading dose of 9 MIU, equivalent to 300 mg of colistin-based activity (CBA), diluted in 100 ml of isotonic serum over 1 h. Immediately after the end of the loading-dose perfusion, the maintenance dose was administered discontinuously 2 times/day, i.e. 4.5 MIU (150 mg CBA) over 1 h every 12 h.

In the presence of renal insufficiency, the loading dose was maintained as mentioned above (9 MIU/300 mg CBA), but the relay doses were adjusted according to the creatinine clearance as the following regimen: 4.5 MIU (150 mg CBA) over 1 h per 24 h if the clearance was between 10 and 30 ml/min and 4.5 MIU (150 mg CBA) over 1 h per 48 h if the clearance was <10 ml/min.

The standard dose-colistin group received CMS i.v. without a loading dose at a dosage of 6 MIU (200 mg CBA) per day over 24 h, continuously by electric syringe. In cases with renal insufficiency, the doses were adapted according to the creatinine clearance as the following regimen: 4 MIU (133 mg CBA) over 24 h by electric syringe if the clearance was between 10 and 30 ml/min and 4 MIU (133 mg CBA) over 48 h by electric syringe if the clearance was <10 ml/min.

Clinical and Biological Assessments

Data were collected by means of a standardized form for both groups, identifying the matching criteria (age, SAPS II and infection site), daily supervision of renal function, time to onset of acute kidney injury (AKI), coadministered nephrotoxic agents, signs of neurotoxicity, clinical and microbiological outcomes, total duration of treatment with colistin and final outcome.

Bacteriological Assessment

Bacteriological sampling was taken from tracheal aspiration, blood or catheter tips. Ventilator-acquired pneumonia (VAP) was defined by a level of $>10^6$ CFU/ml and catheter-related infection by a level of $>10^3$ CFU/ml. Follow-up of these samples was done twice weekly during the period, going from the introduction of CMS till the end of therapy or discharge of the patient.

The isolation of microorganisms was done by routine microbiological methods. Sensitivity to colistin was determined by E test and the isolated strain was considered sensitive when the MIC was <2 mg/l. Multiresistance was defined as resistance to cephalosporins, carbapenems, monobactams, quinolones and aminoglycosides. The susceptibility of strains is tested on a colistin base, and a strain is considered susceptible when the MIC ≤2 mg/l, i.e. 60,000 IU of the colistin base. So the doses employed in this trial were equivalent to 100 times the MIC for the standard-dose group (6 MIU/day) and 150 times the MIC for the loading and following doses for the high-dose group.

Definitions of Outcome Criteria

The efficiency was evaluated by the disappearance of infectious signs and the eradication of microorganisms on all the follow-up cultures.

The definition and severity estimation of AKI was estimated by the AKIN (Acute Kidney Injury Network) criteria [15]. AKI oc-

Table 1. Clinical characteristics of patients

	High-dose colistin group (n = 46)	Standard-dose colistin (n = 46)	p value
Age, years	50.19±17.04	48.91±18.15	0.49
SAPS II	38±12	39.17±12	0.14
Infection site			
VAP	28 (61)	28 (61)	
Bloodstream infection	8 (17.5)	8 (17.5)	
CRI	4 (8.5)	4 (8.5)	
Other	6 (13)	6 (13)	
Coadministered nephrotoxic agents			
Glycopeptides	6 (13)	8 (17.5)	1
ICA	4 (8.5)	3 (6.5)	0.86

Values are expressed as mean ± standard deviation or n (%). CRI = Catheter-related infection; ICA = iodinated contrast agent.

curred when plasmatic creatininemia increased to >1.5 times its base value.

Ethical approval of the study protocol was obtained from the institutional review board/ethics committee of the University Hospital Center of La Rabta.

Statistical Analysis

The sample size was fixed at 46 patients per group. The parameters considered in the calculation were the matching method of the groups, a power of 80%, an error risk alpha of 5%, a judgment criterion defined by a difference in cure rate of at least 20% in favor of the high-dose group and the bilaterality of the statistical tests.

Results were expressed as mean ± standard deviation (for quantitative variables) or percentages (for qualitative variables). Means were compared with the nonparametric Wilcoxon test and the comparison of the percentages with the McNemar χ^2 test.

Analysis was realized with SPSS v20 software. The significance level was set at $p < 0.05$ and all the tests were bilateral.

Results

Ninety-two patients with infections caused by MR GNB requiring colistin therapy were included and distributed into 2 groups by matching. The matching criteria were statistically verified between the 46 pairs of patients and the infection sites were the same in each pair, as shown in table 1.

Thirty patients in the high-dose colistin group (63%) were cured at the end of treatment compared to 41.3% in the standard-dose colistin group, with a superiority that was statistically significant (p = 0.04; fig. 1).

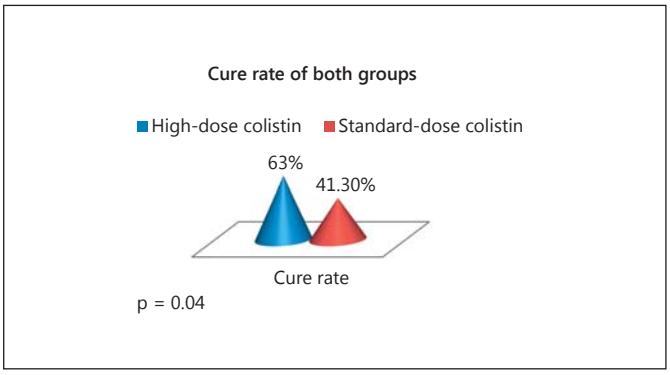

Fig. 1. Cure rate of the 2 groups.

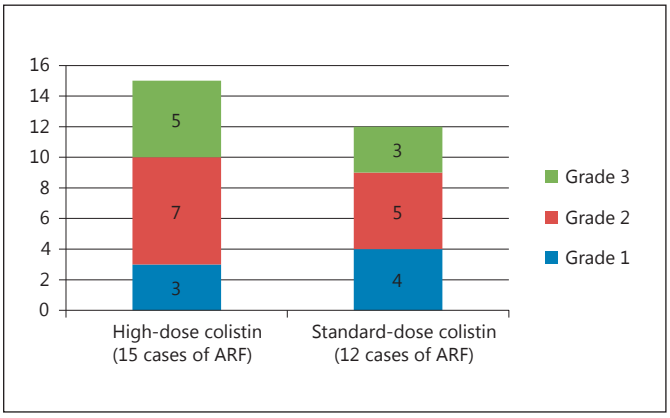

Fig. 2. Distribution of patients in the 2 groups according to the AKIN classification. ARF = Acute renal failure.

The total duration of the 2 therapeutic protocols was similar (13.63 ± 15.63 vs. 8.1 ± 6.3 days; p = 0.25). The occurrence of a second infection with MR GNB was less common in the high-dose colistin group, but this was not significant (4.3 vs. 13%; p = 0.21).

Moreover, we did not find a higher risk of nephrotoxicity from increased daily doses of colistin. AKI was reported in 15 patients in the high-dose colistin group (32.2%) and 12 in the standard-dose colistin group (26%) with p = 0.64. The distribution of these patients according to the severity of renal failure (AKIN classification) was similar (fig. 2). Dose adjustment was necessary for 2 patients in each group.

There was no significant difference as to the time to AKI onset in the 2 groups (p = 1). Peak serum creatinine levels were 752 µmol/l in the high-dose colistin group and 531 µmol/l in the standard-dose colistin group, with re-

Table 2. Outcome parameters of the 2 groups

Studied variables	High-dose colistin group (n = 46)	Standard-dose colistin group (n = 46)	p value
Cure rate	63	41.3	0.04
Duration of treatment, days	13.63±8.1 (12)	15.63±6.3 (15)	0.25
Recurrent infection	4.3	13	0.21
AKI	32.2	26	0.64
Time to AKI onset, days	8.32±4.3 (7)	11±6.4 (9.5)	1
Renal replacement therapy	26.6	41	1
Neurotoxicity	6.5	2.1	0.25
Mortality	23	27.5	0.6

Values are expressed as percentages or mean ± standard deviation (median).

spective clearances of 10 and 18 ml/min. The necessity for renal replacement therapy in the subgroups with AKI was similar for the 2 groups (26.6 vs. 41%; p = 1). Indications were: refractory hyperkalemia (4 cases), anuria (2 cases) and acidemia (2 cases) (table 2).

Axonal neuromyopathy was revealed on electromyogram in 3 patients in the high-dose colistin group, but a causal relationship with colistin was difficult to identify because of the presence of other known factors contributing to such complications (e.g. narcotics, sedatives, corticosteroids, hyperglycemia and hypoalbuminemia). Moreover, there was worsening of pre-existing polyneuropathy in 1 case. One case was recorded in the standard-dose colistin group. The difference was not significant (p = 0.25).

Mortality was 23% in the high-dose colistin group and 27.5% in the standard-dose group, with no significant statistical difference (p = 0.6).

Different comparisons, analyzed with their significance levels, are summarized in table 2.

Discussion

The main finding of this comparative study of matched series is that, in critically ill patients with MR GNB infections, high-dose CMS, prescribed as a 9-MIU loading dose and a 9-MIU maintenance dose twice daily, is more effective than the previous regimen (6 MIU continuously per day). Indeed, the high-dose CMS strategy provides a high degree of clinical cure (63 vs. 41.3%; p = 0.04), with no significant renal or neurological toxicity.

The incidence of MR GNB infections is increasing. A large-scale Greek study focused on the sensitivity of *P. aeruginosa* isolates over 4 years, showing that 56.56% were resistant to ≥3 classes of antipseudomonal antibiotic [6].

Therapeutic drug monitoring to control the administration of colistin is not available in daily ICU practice. This is mainly due to the lack of pharmacoclinical data. The high-dose CMS strategy may have contributed to a high response rate, by increasing the colistin concentration at the infected site. In our series, increasing the daily dose from 6 MIU to a loading dose of 9 MIU followed by 9 MIU every 12 h improved clinical cure rates from 41.3 to 63%. This hypothesis fits well with the results of other studies that have adopted the same colistin dosing regimen. Indeed, the cure rates were 70% in the study by Cheng et al. [16] and 82.1% in the study by Dalfino et al. [12].

Pharmacological dosages of 2 MIU (174 mg) of CMS i.v. every 8 h to critically ill adult patients with VAP showed suboptimal plasma concentrations of colistin, undetectable in bronchoalveolar lavage fluid [17]. The question of the effectiveness of i.v. colistin in pneumonia is being increasingly studied because of its inadequate diffusibility in the lungs; more attention is being paid to administration by aerosol (a study in this direction is currently ongoing in our unit).

Moreover, a fractioned CMS regimen of 9 MIU 3 times daily, currently prescribed in ICU practice, has been associated with suboptimal and delayed steady-state concentrations [11, 18, 19]. Colistin is a concentration-dependent antibiotic with a half-life of 14.4 h, so its administration in 2–3 divided doses contributes to greater efficiency. This has been confirmed by Garonzik et al. [11], who, on the basis of pharmacokinetic/pharmacodynamic analysis of CMS in critically ill patients, suggested that to obtain a steady-state plasma concentration of colistin of 2.5 mg/l, a patient with a weight and a renal func-

tion in the normal range needs to receive a CMS loading dose of 10 MIU followed by a daily maintenance dose of 10 MIU.

Other pharmacological results, such as those of a Greek study, showed that CMS administered at 6 MIU twice daily was associated with a suboptimal ratio of maximum colistin concentration/MIC [20]. A joint pharmacological and microbiological study concluded that the administration of high-dose CMS was an independent factor correlated with microbiological success (adjusted OR 1.74; 95% CI 1.11–2.71; p = 0.015) [21].

In our comparative study, the duration of therapy was longer in the standard-dose colistin group but without significance. The recurrence of another infectious episode caused by MR GNB was observed more in the standard-dose group, also without a significant difference. This may suggest that increased daily doses of colistin for severe infections not only provide better cure rates but also reduce the duration of treatment and therefore the length of stay in the ICU.

Colistin is administered as its prodrug CMS, which undergoes spontaneous hydrolysis to form active colistin [22]. The mechanisms of colistin-induced renal toxicity are unknown, but some investigators have hypothesized that colistin induces membrane permeability and subsequent increases in intracellular cations, anions and water, resulting in cell lysis.

Tubular toxicity has been suggested from microscopic analysis of urine samples and the time course of renal recovery [23–25]; the toxicity develops towards a form of acute tubular necrosis, which is usually reversible. Acute cortical necrosis occurs very rarely. Overall, the incidence of AKI induced by colistin has been overestimated up to now [23–25]. Typically, tubular damage occurs in the first 4 days of colistin therapy and continues for 1–2 weeks afterwards [25].

Renal function returns to its base value after 3–9 weeks [25, 26]. In our study, AKI was observed in 32.2 and 26% of CMS courses in the high- and standard-dose groups, respectively, without a significant difference (p = 0.64). The times to AKI onset were similar (a median of 7 and 9.5 days for the high- and standard-dose groups, respectively). The study of Dalfino et al. [12], who adopted the same CMS regimen, found a lower percentage at 18%. This difference may be explained by early adjustments of CMS administration according to plasmatic dosages, which was not feasible in our series.

Despite the nephrotoxicity induced by colistin, the long-held theory of a dose-dependent relationship between kidney damage and CMS is controversial. Indeed, Hartzell et al. [26] and Ratranaumpawan et al. [27] demonstrated that renal damage depends on daily CMS doses, duration of treatment or cumulative CMS doses. However, Dalfino et al. [12] did not find a correlation between changes in plasmatic creatinine levels and daily doses (Spearman ρ score = 0.004; p 0.98), cumulative doses (ρ = 0.06, p = 0.759) or duration of treatment (ρ = –0058; p = 0.77). In other reports, nephrotoxicity does not appear to be associated with the dose per day (mg/kg/day) but rather with the total cumulative dose [23–25].

The monitoring of renal function and CMS dosage may avoid the worsening of kidney damage. The titration of dose according to colistin's concentration-dependent pharmacodynamic behavior, by extending the dosing interval instead of reducing the single dose, may contribute to the low rate and moderate severity of AKI observed [19].

Therapeutic drug monitoring is not available in daily ICU practice. Therefore, some authors [28] postulate that patients undergoing continuous renal replacement therapy may receive substantially higher doses of colistin (i.e. a high loading dose, followed by a maintenance dose of up to 4.5 MIU twice daily). Treatment can be continued for a prolonged period of time without increasing toxicity. However, this protocol strictly requires the use of filters that enable greater colistin adsorption in the bulk of the membrane, in association with citrate anticoagulation for the prevention of early membrane clogging, in order to also maintain high convection elimination.

It is important to emphasize that other factors play a potentially crucial role in affecting kidney function, such as age, comorbidities, the severity of critical illness, hemodynamic status and coadministered nephrotoxic agents (e.g. glycopeptides and iodinated contrast agent). Indeed, Garnacho-Montero et al. [29] found that the percentage of AKI was significantly greater when CMS was combined with vancomycin than when CMS was prescribed alone (55.2 vs. 28%; p = 0.04). In our series, coadministration of other nephrotoxic agents and CMS could have been involved in the high rates of AKI. However, this did not create a bias in the study because the number of patients who received this combination was comparable in the 2 groups.

The second colistin side effect to consider is neurotoxicity. The exact mechanism of colistin-associated neurotoxicity is not known but is attributed to a presenaptic action of polymyxins that interferes with the receptor site and blocks the release of acetylcholine to the synaptic gap

[30]. Other potential factors may precipitate neurotoxicity, such as renal dysfunction and the concomitant use of muscle relaxants, narcotics, sedatives, anesthetic drugs and steroids [30, 31]. The clinical features of colistin-associated neurotoxicity are not specific and are commonly exhibited by perioral parenthesis, ataxia, delirium and neuromuscular blockade that may lead to apnea. In our 2 groups, the incidence of neurotoxicity was similar (6.5 vs. 2.1%; p = 0.25), i.e. we did not observe an amplified neurotoxicity risk by increasing the CMS dose. However, due to the potential interference of the precipitating factors cited above, we cannot relate this to colistin only. Current studies report a low incidence of colistin-induced neuromuscular toxic events [16, 32]. Falagas et al. [32] concluded that the development of neurotoxicity is probably associated to the duration of the colistin treatment.

Methodological Limitations

The main limitation of our study was the lack of plasmatic dosages of colistin (peak and residual). The reason for this was the unavailability of the recommended method (high-performance liquid chromatography) in the pharmacology laboratory. The trial group (high-dose colistin) was studied prospectively while the control group (standard-dose colistin) was studied retrospectively. This could have generated a bias; it was in order to avoid such a bias that we opted for matching.

Conclusion

This comparative study of matched series of critically ill patients treated with high-dose versus standard-dose CMS for MR GNB infections concluded that: the optimization of CMS dosing to 9 MIU twice daily preceded by a loading dose of 9 MIU can be used with greater efficacy without increasing nephrotoxicity or neurotoxicity. The missing key element was the pharmacological tests: colymicinemia, Cmax, AUC/MIC and percentage of time contact. The results of such tests would be interesting, in order to better define the relationships between the blood level of colistin achieved by the high-dose and the renal function.

Disclosure Statement

The authors confirm that there were no conflicts of interest.

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