Journal of Pharmaceutical Research International

33(16): 62-68, 2021; Article no.JPRI.66502
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

Colistimethate Sodium Dosing and Nephrotoxicity among in-Patients at Tertiary Care Hospital Karachi, Pakistan

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Authors' contributions

This work was carried out in collaboration among all authors. Authors JMA, MTB, US, AH, SS and AJ designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors QAP, SS and AR managed the analyses of the study. Authors AK and MK managed the literature searches. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2021/v33i1631297
Editor(s):
(1) Dr. Asmaa Fathi Moustafa Hamouda, Jazan University, Saudi Arabia.
Reviewers:
(1) Deepak Kumawat, Oriental University, India.
(2) Dalip Singh Rathore, Saurashtra University, India.
Complete Peer review History: http://www.sdiarticle4.com/review-history/66502

Original Research Article

Received 10 January 2021
Accepted 17 March 2021
Published 25 March 2021

ABSTRACT

Introduction: Colistimethate sodium (CMS) is a polymyxin group of antibiotics which were throw out for many years, due to their potential adverse reaction neurotoxicity and nephrotoxicity. The different guidelines were reported regarding CMS dosing some based on Creatinine clearance (CrCl) and some on weight and CrCl. There are many discrepancies in the prevalence of nephrotoxicity that has been reported which included various definitions of acute renal injury and

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many CMS doses used in a variety of literature. In EMA guideline they suggested the dose as 9 MIU which is equivalent to 300 mg of CBA given as a maintenance dose with normal renal function patients. In FDA standard dosing of CMS remains 5 mg/kg CBA per day used and also dose is dependent on patient weight. The aim of this study was to evaluate the dosing criteria of colistimethate sodium associated with nephrotoxicity.

Methodology: A prospective observational study was conducted in private sector tertiary care hospital in Karachi, Pakistan, for duration of six months from July 2020 to December 2020. Sample size was comprised of 157 patients, calculated at 35% prevalence, 95% Confidence Interval and 7% margin of error. Patient included were ≥ 18 years of age, who have received intravenous CMS therapy for greater than 48 hours. Patients having an acute kidney injury or on dialysis (at start of therapy) were excluded. Loading dose and daily dose of CMS was calculated by using actual body weight and Creatinine clearance (CrCl). Cockcroft and Gault equation was used to estimate CrCl before and after the therapy. Nephrotoxicity was assessed by using the RIFLE criteria. SPSS-20 was used for frequency distribution and percentage calculation to show categorical variable.

Results: Among 157 enrolled patients, 101 (64.3%) were male and 56(35.7%) were female (Table 1). Table 2. represents that 68(43.3%) patients were admitted in intensive care unit (ICU) and 89(56.7%) were in medicinal ward; 22.9% patients were in between the age range 60-70 years (Table 3). Among all patients 63(40.1%) patients were at risk of nephrotoxicity, 27(17.2%) patients were developing injury and 14(8.9%) patients were diagnosed to kidney failure and 53(33.8%) patients were found not to developed nephrotoxicity (Table 4). Table 5 exhibits that 48.4% of the patients were receiving dose of CMS using EMA guideline while 51.6% patients were receiving dose of CMS 2.5-5 mgCBA/kg/day according to FDA. Nephrotoxicity was high among FDA regimen (44.5%).

Conclusion: It was concluded that CMS dosing criteria have a significant impact on nephrotoxicity. Close monitoring of renal function, particularly the first week of CMS therapy should be considered to evaluate the renal toxicity of CMS.

Keywords: Colistimethate sodium; neurotoxicity; nephrotoxicity; FDA guidelines; EMA guidelines; Creatinine clearance; multi-drug resistance gram negative bacteria.

1. INTRODUCTION

Colistimethate sodium (CMS) is a polymyxin group of antibiotics which were throw out for many years, due to their potential adverse reaction neurotoxicity and nephrotoxicity [1]. Unfortunately, the incidence of infection caused by multi-drug resistance gram negative bacteria (MDRGNB) like*, "Enterobacteriaceae, Acinetobacter baumannii and Pseudomonas aeruginosa"*. The World Health Organization has announced that this group of bacteria were belongs to the microorganism in the most critical main concern group for research and development of new anti-bacterial agent [2]. With the introduction of polymyxin to clinical practice, CMS was marketed as offering greater or equal anti-bacterial potency as compared to polymyxin B and CMSwas supposed to serious toxic effect in patient because larger dose of CMS were required for effectiveness and thus nephrotoxicity rate were increased [3]. Acute kidney injury(AKI) is a potential life threatening condition, approximately 7% of all hospitalized patients developed AKI with the higher prevalence in intensive care unit about 20% [4]. In particular, acute kidney injury (AKI) is considered to be dose and duration dependent and it is expected to occur in approximately 15%-25% of cases receiving CMS therapy. The pathophysiology of colistin-associated nephrotoxicity is multifactorial [5]. The incidence of AKI during treatment is related with worse prognosis, including higher mortality rates [6,7]. Among patients who were prone to AKI during CMS treatment has been higher incidence of chronic renal failure [8]. The RIFLE criteria (risk.injury.failure.end stage kidney disease) is anauthorized tool used in literature to estimate drug induced AKI [9,10].

The dose of intravenous CMS is recommended by the manufacturers in the "united states" is 2.5-5 mg/kg of colistin base that is "75,000-150,000IU/kg" per day divided into 2-4 equal doses. For adult patients with normal kidney function. The dosage of united kingdom is "4-6 mg/kg(50,000-75,000 IU/kg)"per day with body weight less than and equal to 60kg in three divided doses for adults [11]. Registered brands of Colistimethate Sodium used in Pakistan are; Coliate (One MIU), Colistim (One MIU).Its each vial contains Colistimethate Sodium (80 mg) and

colistin base activity (CBA) is 30 mg which is also equal to One Million International Units (MIU) per vial Colistimethate Sodium. Its intravenous administration is to be prepared in 0.9% normal saline or 5% dextrose water (100ml) at run rate of 30 minutes [12]. The different guidelines were reported regarding CMS dosing some based on creatinine clearance (CrCl) and some on weight and (CrCl).There are many discrepancies in the prevalence of nephrotoxicity that has been reported which included various definitions of acute renal injury and many CMS doses used in a variety of literature [13]. In EMA guideline they suggested that (9MIU) which is equivalent to 300 mg of CBA given as a maintenance dose with normal renal function patients. In FDA standard dosing of CMS remains 5 mg/kg CBA per day used and also dose is dependent on patient weight. Although the package insert recommended dose based on IBW (ideal body weight) but few active clinicians prefer to use the body weight of patients or an adjusted body weight for achieve higher serum concentration [14]. The FDA and EMA update their dosing recommendation in 2014 significant variation exists in their dosing regimen, the EMA regimen included 9MU maintenance dose and based on CrCl to achieve a desired steady-state concentration of CMS as compared with FDA [15,16]. In this study, we examined the incidence of CMS induced nephrotoxicity in our patient's population and evaluated the association between CMS dosing and the incidence of nephrotoxicity. The aim of this study is to evaluate that which risk factors and dosing regimen effect nephrotoxicity.

2. METHODOLOGY

This was a prospective observational study conducted at Tertiary Care Private Sector Hospital in Karachi, Pakistan, among patients, who were prescribed with intravenous Colistimethate Sodium. Clinical data was obtained from the In-patients' bed side file. Patients were enrolled after having informed consent. The therapy with CMS was noted at the start of antibiotic (Colistimethate Sodium) till the patient health recovered or discharged from hospital. Demographic data included age, gender, weight of the patients. Loading dose and daily dose of Colistimethate Sodium was calculated by the Principle Investigator, using actual body weight and Creatinine clearance (CrCl). Cockcroft and Gault equation was used to estimate CrCl before and after the therapy [17]. Nephrotoxicity was assessed by using the RIFLE criteria [9,13,18]. Duration of the study was 6 months from July 2020 to December 2020. Sample size of 157 In-patients was calculated at 35% prevalence, 95% Confidence Interval and 7% margin of error [19]. In-patient with age ≥ 18 years and were prescribed intravenous Colistimethate Sodium therapy for greater than 48 hours, were included. Patients who have Colistimethate Sodium therapy only one admission episode were not included in the study. Patients who were pregnant, or received inhaled colistin therapy and patients having an acute kidney injury or on dialysis at start of therapy were also excluded. SPSS-20 was used for data analysis. Frequencies and percentage were calculated.

3. RESULTS

Among 157 enrolled patients, 101 (64.3%) were male and 56(35.7%) were female (Table 1). Table 2 represents 68(43.3%) patients were admitted in intensive care unit (ICU) and 89(56.7%) patients were admitted in medicinal ward; 22.9% patients were in between the age range 60-70 years (Table 3). Among all patients 63(40.1%) patients were at risk of nephrotoxicity, 27(17.2%) patients were developing injury and 14(8.9%) patients were diagnosed to kidney failure and 53(33.8%) patients were found not to developed nephrotoxicity (Table 4). Table 5 exhibits that 48.4% of the patients were receiving dose of CMS using EMA guideline while 51.6% patients were receiving dose of CMS 2.5-5 mgCBA/kg/day according to FDA. Nephrotoxicity was high among FDA regimen (44.5%).

4. DISCUSSION

Nephrotoxicity is a major cause of high mortality and morbidity worldwide [20]. Nephrotoxicity

Table 1. Gender of patients

Gender	Frequency	Percent
Male	101	64.3
Female	56	35.7
Total	157	100.0

Table 2. Patients' admission in wards

Admission Ward	Frequency	Percent
Intensive Care Unit	68	43.3
Medicinal Ward	89	56.7
Total	157	100.0

Table 3. Age of patients

Age of patients	Frequency	Percent
18-28 year	9	5.7
29-38 year	15	9.6
39-48 year	24	15.3
49-58 year	26	16.6
59-68 year	28	17.8
69-78 year	36	22.9
79-88 year	17	10.8
89 or Above	2	1.3
Total	157	100.0

Table 4. Rifle criteria of patients

Rifle criteria	Frequency	Percent
No Risk	53	33.8
Risk	63	40.1
Injury	27	17.2
Failure	14	8.9
Total	157	100.0

Table 5. Dose calculation strategy of CMS

No. of Patients	CMS Dose 3MU Every 8 Hourly(EMA)	CMS Dose 2.5-5mgcba/Kg/Day(FDA)
157	76(48.4%)	81(51.6%)
Rate of Nephrotoxicity	34(21.6%)	70(44.5%)

related to CMS administration is a major challenge for clinicians now-a-day. As shown in Table 2, 43.3% patients were admitted in ICU and 56.7% patients were admitted in medicinal ward, however, Omrani et al. expressed admission in ICUas the main independent factor [21]. Our study revealed that male ratio was significantlyhigh as compared to female in diagnosis of kidney injury; males are more prone to nephrotoxicity. Rauf et al. study also reported that males had a high rate of acute kidney injury [22]. Inanother study of Horkanet al. they found a significant association between sex and acute kidney injury [23]. Inour study, the increase rate of nephrotoxicity was found in age group 40-80years. Chao et al. also reported that in CMS administration the frequency of nephrotoxicity was also high in old aged patients because of age related functional deterioration of kidney [24]. Rodrigoet al. found that age related factor is more prone to kidney injury. They also stated that mechanical ventilation and glomerular filtration rate are independent predictors of nephrotoxicity associated with CMS [25].

In a present study, we included total 157 patients in which 63(40.1%) patients were at risk of nephrotoxicity, 27(17.2%) patients were develop injury, while 14(8.9%) patients were diagnosed to kidney failure and 53(33.8%) patients did not developed nephrotoxicity (Table 4). Pogue et al. reported 17% rate of injury which is similar to our study. They concluded that predictor of nephrotoxicity is due to high dose greater than and equal to 5 mg /kg/day [14]. In another study of Al-Abdulkarim et al. 40.6% patients were on risk which is very close to our study, they also stated that nephrotoxicity increased due to inappropriate dosing and elderly age [10]. In our study we found that 153(97.5%) patients were

receiving 9MU loading dose following (3MU) CMS every 8 hourly which is equivalent to 300 mg CBA/day. It was found that 48.4% of the patients were receiving the dose of the drug based on EMA guideline and 51.6% patients were receiving the dose based on CMS 2.5-5 mg CBA/kg/day according to FDA (Table 5). It was observed that clinicians prefer different dosing criteria; some were preferring according to creatinine clearance (CrCl>80 ml/min CMS dose 300 mgCBA/day) and some were preferring 2.5-5 mg/kg/day and use actual body weight for dose calculation instead of ideal body weight. In this study we found that nephrotoxicity was high in patients who were prescribed according to FDA regimen (44.5%), which may be due the reason that the dose is adjusted according to serum creatinine or CrCl and using actual body weight instead of using ideal body weight, high dose given to patient in aspect of creatinine clearance (CrCl). Our study revealed that 15 patients had low CrCl before therapy but were receiving high dose of CMS. Falagas et al. also concluded that administration of CMS dose was statistically correlated with serum creatinine [11]. Among patients, who received dose according to EMA criteria, their dose should be adjusted according to creatinine clearance. In a study of Almutairy et al. the incidence of CMS associated nephrotoxicity was high due higher daily dose of CMS. They stated that more than 75% of the patient were on stage 1 and stage 2 AKI [26]. In another study of Omrani et al. high dose of CMS therapy associated with high rate of nephrotoxicity [21]. De Ryke et al. study also reported that daily high dose of CMS increased the incidence of nephrotoxicity and was using actual body weight for dose calculation, similar to our study, they also stated that use of ideal body weight for calculating the dose may be less nephrotoxic [27].

5. CONCLUSION

It was concluded that Colistemethate Sodium dosing criteria was found to have significant impact on nephrotoxicity. It was recommended that close monitoring of renal function, particularly the first week of CMS therapy should be consider evaluating the renal toxicity of CMS. Dose should be calculated on the basis of ideal body weight and creatinine clearance of the patients to avoid the risk of nephrotoxicity. Further analysis must be carry on to recognize the optimal dose of CMS for the purpose of safety, efficacy and toxicity.

CONSENT

Patients were enrolled after having written informed consent.

ETHICAL APPROVAL

Ethical approval was taken from Ethics Review Committee (ERC) of Ziauddin University (Protocol No. 1820120JAPHA).

ACKNOWLEDGEMENT

We are thankful to the management of Dr. Ziauddin Hospital and Ethics Review Committee for supporting the study.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle4.com/review-history/66502