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Simulation Approach for Dosage Optimization of Colistimethate Sodium in Critically Ill South Indian Patients - A Pilot Study

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Abstract

Rationale use of antibiotics has become a global need with the existence of only a handful of antibiotics and rapid emergence of the antibiotic resistant microbial strains over the past two decades. Management of infections in critically ill patientswith drug resistance is a major healthcare challenge and Colistin (Polymyxin E) is one such last-resort antibiotic that is extensively being utilised as a salvage therapy in these patients. The present study aimed to estimate the primary pharmacokinetic (PK) parametersofColistin from plasma concentrationsobtained from eight critically ill renal compromised patientsby the conventional two-stage approach and suchparameters were leveraged to simulate the plasma drug concentrations with Creatinine clearance (CrCl)as a covariate.Primary PK parameters (Clearance (CL) and Volume of Distribution (V)) were found to be 9.29 L/h and 13.92 L respectively.Further simulations for 90 subjects with three ranges of CrClrevealed a wide deviation from the target concentration of Colistin with peak and trough plasma concentrations(mg/L) 2.05±0.95, 3.07±1.18, 5.45±2.16 and 0.39±0.28, 0.98±0.52, 1.85±1.73 respectively in the three groups with declining CrCl. These findings reinforce the need to perform TDM and dose optimization of colistin in critically ill patients.

Keywords: Colistin, critically ill patients, dosage optimization, pharmacometrics,simulation, Indian

Introduction

The past two decades have witnessed a remarkable increase in the antibiotic resistance especially in the gram-negative bacteria such as *Pseudomonas Aeruginosa*, *Acinetobacter Baumannii*, and *Klebsiella Pneumonia* that contribute majorly to the healthcare burden (Martin & Yost, 2011). It is crucial to optimize the dosing of antibiotics to improve the attainment of the of pharmacokinetic/pharmacodynamic (PK/PD) targets and achieve better clinical outcomes. The infections in critically ill patients contribute majorly to morbidity and mortality despite the treatment advances due to the high probability of recruitment of drug resistant strains and complex pharmacokinetics in the critically ill. This potentially leads to highly variable antimicrobial exposures leading to either antibiotic toxicity or treatment failures especially in antibiotics with narrow therapeutic index(Tosi et al., 2018),(Thummel &Lin, 2014). Intricate dosing of the antibiotics in critically ill patients with severe infectionsremains as a challenge for the clinicians as understanding the basis for drug disposition and response variability is essential to move beyond the era of empiricalone size fits all approach for dose selection into an age of personalized medicine to attain the therapeutic goals(Whiting et al.,1986), (Agyeman &Ofori-Asenso,2015).

Colistin (also called polymyxin E) is a narrow therapeutic index antibiotic with a concentration dependent bactericidal activity against *P.Aeruginosa* and *A. Baumannii* and is being increasingly used in recent days in the salvage therapy of severe infections due to Gram-negative bacteria in critically ill patients (Sayed Ahmed et al.,2020; Nation &Li,2009).Colistin binds to lipopolysaccharides and phospholipids in the outer cell membrane of Gram-negative bacteria and competitively displaces divalent cations from the phosphate groups of membrane lipids, leading to disruption of the outer cell membrane, leakage of intracellular contents, and bacterial death. In addition, it can also bind and neutralize lipopolysaccharide (LPS) and prevent the pathophysiologic effects of endotoxin in the circulation (Warren et al.,1985). Formulations containing Colistimethate sodium (CMS) which is a prodrug that is hydrolysed after IV administration to produce derivatives, including the active drug Colistin are available for parenteral use. The ideal dose for Colistin remains uncertain but when used in critically ill patients, an initial loading dose of 9 million international units of Colistimethate sodium (270 mg Colistin base) is suggested. The adverse drug reactions are Nephrotoxicity, Neurotoxicity and Hypersensitivity (Lim et al., 2010). The importance of preventing drug resistance to

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colistin, the narrow therapeutic window & significant toxic potential of the drug and high variability in drug exposures drives the need to perform therapeutic drug monitoring and pharmacokinetic studies in critically ill patients. Neither the pharmacokinetic studies nor the dosage guidelines are available for such patients in India. Therapeutic drug monitoring may represent a useful clinical tool to optimize individual dosage and plasma concentrations, possibly optimizing the antibacterial effect, minimizing the emergence of resistance and reducing Colistin induced side effects (Dijkmans et al.,2015), (Plachouras et al.,2009).Data on the pharmacokinetics of IV CMS in critically ill patients are limited (Karnik et al.,2013).This open label study was designed to prospectively obtain the plasma concentrations of colistin in critically ill patients of south India to estimate the population pharmacokinetic parameters of Colistin and to propose an optimal dosage based on further simulations.

Methodology

Critically ill patients including those on haemodialysis, admitted in ICU of M/s. Rajagiri Hospital, Chunangamvely, Aluva, Kerala, South India between during December 2016 to January 2017 treated with Colistin were enrolled in this study after getting written informed consent / assent.The study was approved by the Institutional Ethics Committee. Pregnant women, lactating mothers, paediatric patients, patients with known liver disease and those who are not of South Indian origins were all excluded.

The doses of the Colistin were empirically decided by the physician based on the type and severity of infection.26blood samples with a minimum of 3 samples per subject were collected from 8 patients at any of the following nominal times: pre dose, 0.5, 1, 2, 4, 8, and 12 h after administration of Colistin. Demographic and clinical data were collected for all subjects.The blood sample was centrifuged at 4000 rpm for 15 minutes and the plasma supernatant was separated and stored at -80°C till further analysis.The plasma samples were analysedbya validated high performance liquid chromatography- tandem mass spectroscopy (LC-MS/MS) to quantify the Colistin concentration.

Colistinplasma concentration data and other demographic data of the study patients were tabulated as a data file in a specific format required by the PKSolver, an add-on macro for MS Excel and the primary pharmacokinetic parameters from the plasma concentration versus time for 8 patients were obtained by the traditional two-stage approach, i.e., the individual clearance(CL/F) and volume of distribution(Vd) for each patientwere derived from data of minimum 3 samples fitted to one compartment model was first calculated and then the mean value of the parameters were estimated as the population parameters.

The CL/F and Vd estimates of the two-stage approach was used to simulate the plasma drug concentrations with creatinine clearance as a covariate using the PUMAS software (version 1.40.1). Three population groupswith 30 subjects in each group were built with the creatinine clearance values of 60-89ml/min, 30-59ml/min and 15-29ml/min in group A, B and C respectively. Loading dose of 9MIU infused over 30 minutes and maintenance dose of 3.2MIU infused over 30 minutesevery 12 hours after the loading dose that was traditionally used in the study subjects was adopted for the simulation. The therapeutic range of 2-2.5 mg/L was used as target to optimise the dosage regimen of Colistin.

Results

A total of 12 subjects screened on the basis of inclusion and exclusion criteria and eight patients were recruited into the study and allof them (100%) completed the study, out of which 75% (n=6) were male**.** Thedemographic details of the patients are summarised(Table 1). The age of the patients in this study ranged between 43 - 82 years with a mean of60.13±14.14**.** The serum creatinine ranged from 0.5-4.46 mg/dL with a mean of 1.48±1.34.

Table1: Demographic data of patients

ID	Age (Years)	Gender	Serum Creatinine (Mg/Dl)	Dialysis Status	Diagnosis	Bacterial Profile	Outcome
1	43	M	1.03	NO	Road traffic accident	*Pseudomonas Spp.*	Survived
2	47	M	2.38	NO	Exfoliative dermatitis, Secondary MRSA infection	*Methicillin -resistant Staphylococcus Aureus*	Died
3	82	M	4.46	YES	CKD, Pulmonary oedema	*Acinetobacter Spp.*	Died
4	61	M	1.21	NO	Viral Fever with leukopenia	ESBL MDR *Klebsiella*	Survived
5	56	M	0.79	NO	Bronchopneumonia, Breathlessness	*Pseudomonas Aeruginosa*	Died
6	50	F	0.5	NO	Pneumonia	*Acinetobacter Spp.*	Survived
7	78	F	1	NO	Cerebrovenous accident	*Pseudomonas Spp.*	Survived

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8	64	M	0.5	NO	Acute respiratory distress syndrome	*Acinetobacter Baumannii and Pseudomonas Spp.*	Died

The dose, frequency and infusion time of CMS were recorded(Table-2)andthe mean dose of CMS administered was found to be 3.2±1.29 MIU.

Table2: CMS administration and sampling data

Patient ID	Dose (MIU)		Frequency	Infusion Time (Hr)		
	Loading	Maintenance		1st	2nd	3rd
1	9	4.5	BD	0.5	0.5	0.5
2	9	2	BD	1	1	NIL
3	9	2	BD	1	1	0.5
4	9	4.5	BD	0.5	0.5	1(3MIU)
5	9	4.5	BD	0.5	0.5	NIL
6	9	4.5	BD	0.5	0.5	0.5
7	9	4.5	BD	1	1	0.5
8	9	2	BD	1	1	0.5

The mean primary PK parameters,CL/F and V estimated by the two-stage approach with PKSolverwere found to be 9.29 L/h and 13.92 L respectively.Further, simulations for 90 subjects for the maintenance dose with the three ranges of CrClrevealed a wide deviation from the target concentration of colistin with peak and trough plasma concentrations(mg/L) of2.05±0.95, 3.07±1.18, 5.45±2.16 and 0.39±0.28, 0.98±0.52, 1.85±1.73 respectively in the three groups with declining CrCl(Figure 1). One-way ANOVA showed a statistically significant difference between the plasma concentrations of the 3 groups with a p value of <0.001. The peak concentrations were achieved between 3-4h after the maintenance dose and 1 hour after the loading dose. Additionally, it was noted that the peak plasma concentration was exceptionally high after the loading dose i.e., 10.8±3.89 (Figure 2).

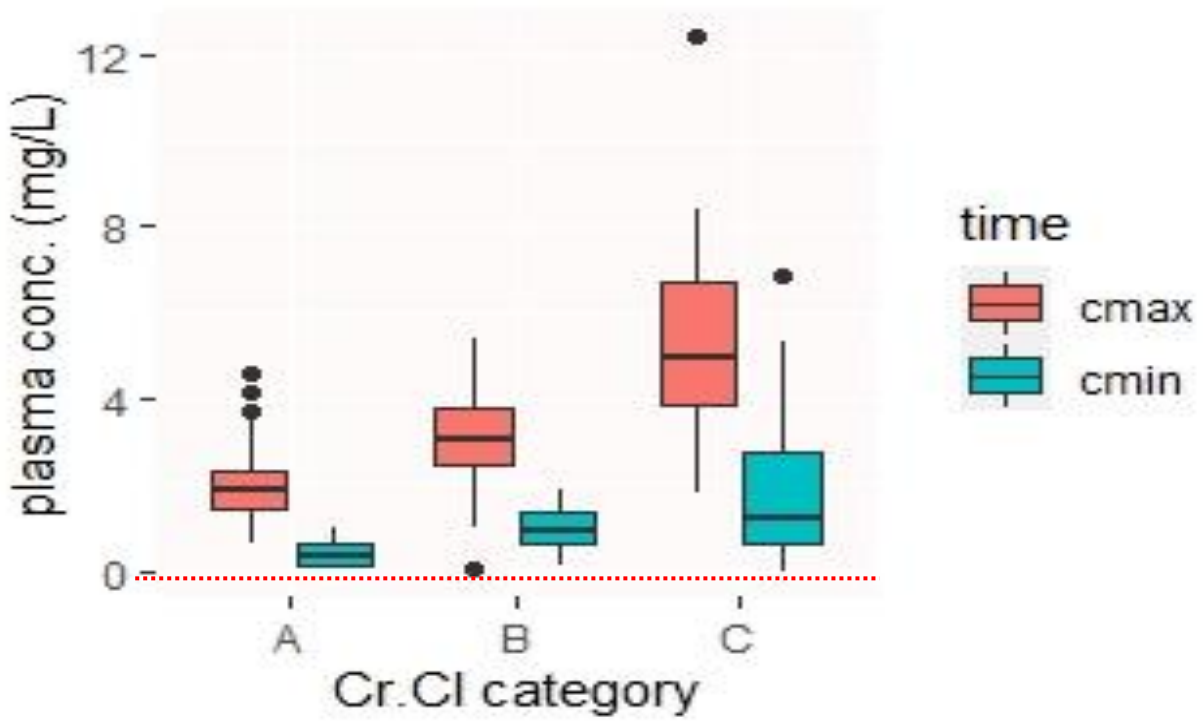

Figure 1:Peak and trough plasma concentrations of 30 subjects in each group with Creatinine clearance values of 60-89ml/min, 30-59ml/min and 15-30ml/min respectively in group A, B and C.

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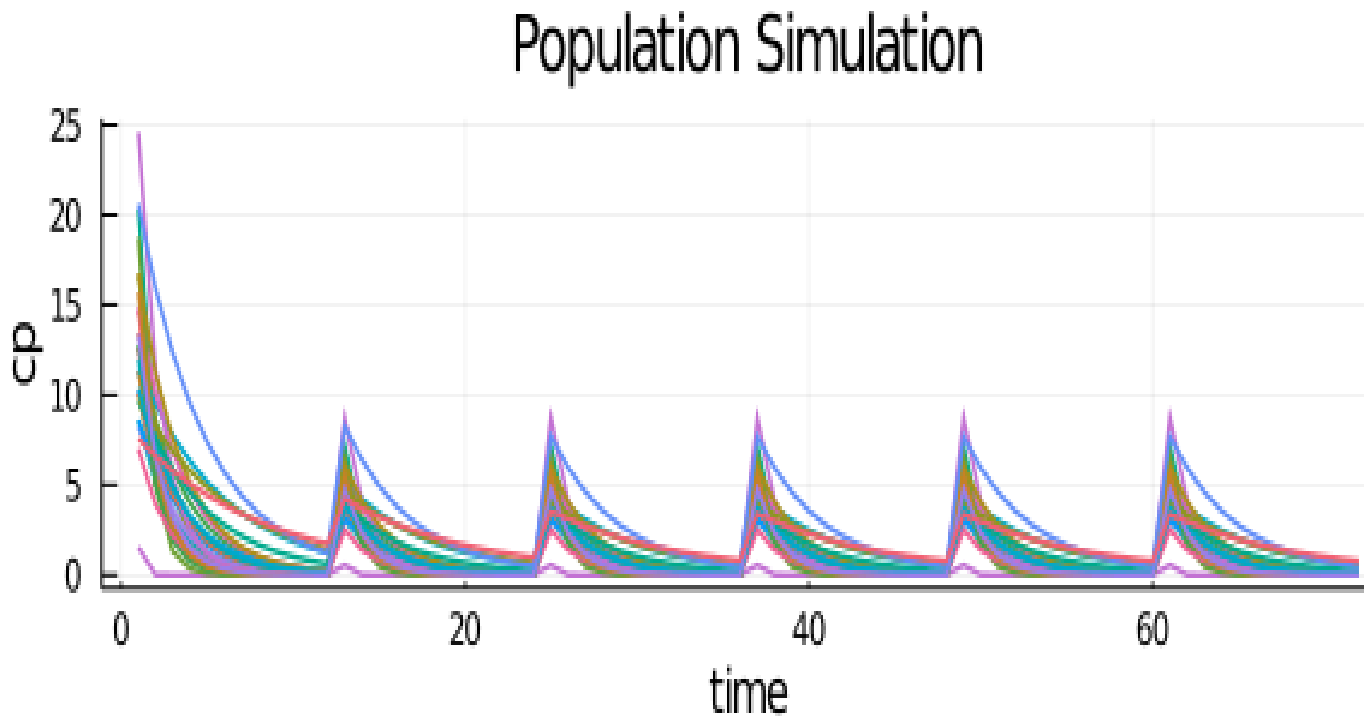

Figure 2:SimulatedTime Vs Plasma concentration profile following the loading doseat 0 hour followed by the maintenance dose after every 12 hours.

Discussion

The findings this study and estimated primary PK parameters are fairly in accordance with the values reported in the literature. Previous studies have elucidated that despite the advantage of high bactericidal effect and early attainment of steady state at higher steady state concentration and administration of loading dose, this may possess the risk of deteriorating renal function due to its nephrotoxic potential (Mohamed et al.,2012), (Karaiskos et al.,2015), (Garonzik et al.,2011), (Grégoireet al.,2014). It is evident from this study that the plasma concentrations are highly variable among the critically-ill patients with altered renal function and the empirical dosing of the antibiotics merely by the clinical judgement potentially leads to high deviations from the intended PK/PD goals. It was suggestive from further simulations that administration of the maintenance dose 24h after the loading dose and logical dose reductions based on the plasma concentrations by performing Therapeutic Drug Monitoring may enhance the pharmacokinetic and health outcomes.

Conclusion

The primary PK parameters of Colistin in south Indian population estimated in this study followed by the simulation experiments revealed that there is a need to adjust the dosage regimen of CMS based on the renal function of the critically ill patients. Also, performing therapeutic drug monitoring of Colistin in these patients will help optimizing the dosage regimen of CMS and thereby minimize the risk of nephrotoxicity by the drug. The findings of this study will be used to lay the groundwork for future studies (ongoing research with a broader sample size) into Colistin dosing optimization using pharmacokinetic and pharmacodynamic principles.

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Availability of data and other materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request. Please mail and reach us in kparun@jssuni.edu.in

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Ethics approval and consent to participation

The study was approved by the Institutional Ethical Committee – Healthcare & Medical Research (IEC) of Rajagiri Hospitalwith Approval No. RIEC/2017/006. Written informed consent / assent were obtained from all participants. The privacy and confidentiality of all the participants was strictly maintained.

Competing interests

The authors declare no conflict of interest.

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