Colistin in critically-ill patients on sustained low-efficiency dialysis: implications for dose selection

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Background and rationale

Colistin, usually administered as an inactive prodrug called colistin methanesulfonate (CMS), is often used as a last resort therapy against multidrug-resistant Gram-negative pathogens (1, 2). Since colistin was first developed in the 1950s, before the modern pharmacokinetic/pharmacodynamic guidelines for approval were established, there is still a lack of information on the appropriate use of this antibiotic in specific patient populations. For example, there is still a paucity of information on suitable dosing regimens of CMS for patients undergoing sustained low-efficiency dialysis (SLED) (3). Additionally, the International Consensus Guidelines for the Optimal Use of the Polymyxins have emphasised the need for more information on the use of intravenous CMS in patients requiring SLED for renal support (3). Frequently, patients undergo SLED on a daily basis; however, it is not a continuous form of therapy (4). The intermittent nature of SLED, and associated changes in the PK of renally cleared antibiotics, increase the risk of underdosing and overdosing of prescribed antibiotics, such as colistin (5). Notably, the population pharmacokinetic (popPK) approach is able to capture the time-dependent changes in total clearance due to the intermittent nature of SLED and allows for precise dosing optimisation (6).

Hypothesis

Population pharmacokinetic (PK) modelling will elucidate the effect of SLED on the disposition of colistin to enable design of optimised dosing regimens for patients undergoing SLED.

Aims

1. To develop a population PK model that describes and predicts the effect of SLED on the PK of colistin in patients with renal impairment.
2. To use Monte Carlo simulations to propose optimised dosing regimens for critically ill patients undergoing SLED to achieve target concentrations of colistin.

Methodology

Thirteen critically-ill patients undergoing SLED for renal support (6-8h) were included in a prospective popPK study. The study employed a cross-over design where the pharmacokinetics of CMS and colistin were studied on both a SLED day (day when SLED was administered) and a nonSLED day (when SLED was not administered). On a nonSLED day, patients received a single dose of CMS [150 mg colistin base activity (CBA)]. On a SLED day, patients received 150 mg of CBA 12-hourly. CMS and colistin plasma concentrations were measured by high-performance liquid chromatography and analysed using the popPK approach (NONMEM [v7.4]). Monte Carlo simulations (MCS) for CMS dosing regimens evaluation were performed. The MCS performed evaluated the probability of target attainment (PTA) defined as percentage of patients achieving relevant average colistin plasma concentration (C_{avg}) targets: >80% for C_{avg} ≥2, >90% for C_{avg} ≥1.5 and <30% for C_{avg} ≥4 mg/L for the first 24h of therapy initiation on a SLED or nonSLED day as well as maintenance therapy.

Results

The disposition of colistin was best described by a one-compartment popPK model. The population mean apparent colistin body clearance, not including SLED clearance, was 1.69 L/h (20.6% inter-individual variability [IIV], 42.1% inter-occasion variability). The apparent colistin SLED clearance was 3.49 L/h (41.7% IIV). The apparent volume of distribution was 50.2 L (23.0% IIV). Additionally, there was no relationship identified between evaluated patient characteristics and the pharmacokinetic parameter estimates for colistin. The MCS performed enabled CMS dosing regimen optimisation and proposed dosing regimens which clinicians can use to guide safe administration of colistin in patients on SLED (**Table 1**). Moreover, the SLED clearance of colistin was estimated directly from respective concentrations in plasma and dialysate (and the flow rate of dialysate) for each participant. The resulting SLED clearance of colistin was 3.23 ± 1.29 L/h (average ± SD), which agreed very well with the SLED clearance of colistin estimated *via* the popPK approach.

Table 1: Example table of PTA of C_{avg} targets across the first 24 h with CMS regimens initiated on SLED and nonSLED days.

Colistin base activity loading dose (LD) and maintenance dosing across the first 24 h	SLED duration
Initiation on a nonSLED day	
LD of **150mg followed 12h later by 50mg**, then after another 12h the relevant maintenance dosing regimen for a nonSLED or SLED day*	-
Initiation on SLED day	
LD of **150mg followed 12h later by 75mg**, then after another 12h the relevant maintenance dosing regimen for a nonSLED or SLED day*	6h
LD of **160mg followed 12h later by 80mg**, then after another 12h the relevant maintenance dosing regimen for a nonSLED or SLED day*	8h
LD of **180mg followed 12h later by 90mg**, then after another 12h the relevant maintenance dosing regimen for a nonSLED or SLED day*	10h

* data not shown

Conclusions

In summary, the developed population PK model provides, for the first time, a comprehensive characterisation of the disposition of formed colistin during SLED based on systemic plasma concentrations and concentrations in dialysate. The findings suggest that a higher dose should be administered on days when SLED is undertaken as compared to non-dialysis days. I was able to provide data to inform CMS dosing in patients requiring intermittent use of SLED, including selection of loading and maintenance doses and different durations of SLED sessions, to achieve relevant PTA to maximise the likelihood of bacterial killing and minimise the risk of nephrotoxicity.

Statement of the scientific innovation and significance of the study

The study presented herein was the first population PK study of colistin to exclusively include patients on SLED and address the recommendation of the International Consensus Guidelines for the Optimal Use of the Polymyxins (2019) for more research on colistin dosing in patients undertaking SLED (3). Prior to the current study, there had been no population PK model, for CMS and/or colistin disposition, developed exclusively in patients undergoing SLED that could lead to a comprehensive dosing guideline for this group of patients. The analysis described is a significant contribution to the knowledge on the optimal use of colistin in this specific patient population, and is currently being used in the preparation of the updated version of the International Consensus Guidelines for the Optimal Use of the Polymyxins. Additionally, the results from this research were featured in press releases and news items in Australia and Thailand.

Statement on the nominating student's specific role in the study

In this project I was responsible for data analysis, interpretation and visualisation, development and validation of the population pharmacokinetic model, Monte Carlo simulations and dosing regimen optimisation.

Declaration

"We declare that this document was prepared primarily by the nominating student and has undergone minimal corrections by the supervisor or any other author on the accompanying abstract."

Student's name: Dominika Fuhs Student's signature: Dominika Fuhs

Date: 06/05/2026

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