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CLINICAL TRIAL REPORT

Pharmacokinetics and Renal Safety Evaluation of Colistin Methanesulfonate Sodium in Korean Healthy Male Volunteers: An Open-Label, Multiple-Dose Study

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Purpose: The objective of this study was to evaluate the pharmacokinetics and renal safety of colistin methanesulfonate sodium (CMS) following single and multiple intravenous administrations in healthy Korean male volunteers. This study provides pharmacokinetic and safety information on an Asian population, where data on polymyxins remain limited.

Patients and Methods: This open-label, single- and multiple-dose pharmacokinetic study enrolled 12 subjects, 11 of whom received CMS, and one withdrew prior to dosing. Five doses of CMS 150 mg potency (equivalent to 150 mg colistin) were administered over 2.5 days as 1-h infusions every 12 h, diluted in 50 mL of normal saline. Serial blood samples were collected at predetermined time points to measure plasma colistin concentrations using a validated liquid chromatography-tandem mass spectrometry method. Renal safety was assessed through serial measurements of serum creatinine, blood urea nitrogen, and renal biomarkers. Serum biomarkers included cystatin C and neutrophil gelatinase-associated lipocalin (NGAL), while urinary biomarkers included clusterin, kidney injury molecule-1, N-acetyl-β-D-glucosaminidase, and NGAL.

Results: CMS reached peak levels rapidly with minimal accumulation (accumulation index 0.91 [95% CI, 0.80–1.03]) and a consistent half-life of 2.3 h after both single and multiple dosing, whereas colistin showed progressive accumulation (accumulation index 1.4 [1.32–1.48]) and a half-life increase from 3.6 to 4.5 h. Renal biomarkers, including creatinine, blood urea nitrogen, cystatin C, and NGAL, showed no clinically relevant changes. Although urinary markers were transiently elevated, they remained within reference ranges throughout the study period. Overall, repeated CMS administration was well tolerated, and no evidence of nephrotoxicity was observed.

Conclusion: Intravenous administration of CMS resulted in evaluable pharmacokinetic profiles in healthy Korean male volunteers. Although no biomarker-based evidence of nephrotoxicity was detected, these findings should be interpreted with caution, given the small sample size and short study duration. These results may support evidence for renal safety assessments in future studies.

Keywords: colistin, pharmacokinetics, renal safety, healthy volunteers

Introduction

The growing prevalence of antimicrobial resistance has considerably diminished the effectiveness of conventional antibiotics in treating patients with bacterial infections.[1] Most notably, multidrug-resistant (MDR) Gram-negative pathogens, collectively known as ESKAPE (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae,*

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Acinetobacter baumannii, Pseudomonas aeruginosa, and *Enterobacter* spp)., have emerged as major clinical threats owing to their remarkable ability to evade the effects of most currently available antibiotics.[2,3]

The limited availability of therapeutic options has renewed interest in older antibiotics, including colistin, which has fallen out of clinical favor owing to concerns regarding nephrotoxicity.[4] Colistin, also known as polymyxin E, is a cationic decapeptide antibiotic originally isolated in 1949 from *Bacillus polymyxa*.[5] Currently, colistin is administered as colistin methanesulfonate sodium (CMS), an inactive prodrug hydrolyzed in vivo to the active colistin base.[6]

Colistin exerts bactericidal effects by interacting with the lipopolysaccharide (LPS) component of the outer membrane in Gram-negative bacteria. Colistin disrupts the bacterial outer membrane through electrostatic interactions and displacement of divalent cations (calcium and magnesium), thereby enhancing permeability, promoting the leakage of intracellular contents, and ultimately resulting in bacterial cell death.[7] Additionally, colistin exhibits anti-endotoxin activity by binding to the lipid A moiety of LPS and neutralizing its toxicity; however, the clinical relevance of this effect remains elusive, as endotoxins rapidly bind to the LPS-binding protein and cell-surface CD14.[4]

Colistin is considered a last-resort therapeutic for MDR Gram-negative infections, such as those caused by *P. aeruginosa, A. baumannii*, and *Enterobacteriaceae*,[4] with a narrow therapeutic window and substantial nephrotoxicity limiting its clinical utility.[8] Pharmacokinetic/pharmacodynamic analyses have identified the ratio of the free area under the concentration (fAUC)–time curve to the minimum inhibitory concentration (MIC) as the most reliable predictor of colistin efficacy, demonstrating a stronger correlation with bactericidal effect than other indices such as Cmax/MIC or time above MIC.[9] In murine models, fAUC/MIC values of 13.6 and 12.9 were shown to correspond to a 1-$\log_{10}$ reduction in the bacterial burden in thigh and lung infection models, respectively.[9]

The initial daily maintenance dose of colistin should target an average steady-state plasma concentration (Css,avg) of 2 mg/L, based on preclinical infection models, clinical pharmacokinetic/toxicodynamic data linking colistin exposure to the risk of acute kidney injury, and the frequent unavailability of pathogen MIC at therapy initiation.[10] This target is suitable for infections caused by organisms with colistin MICs ≤2 mg/L.[10] However, effective antibacterial concentrations substantially overlap with those associated with an increased risk of colistin-induced nephrotoxicity, underscoring the importance of careful dosing when initiating therapy.[11]

Nephrotoxicity remains a major limitation of colistin therapy, with a reported prevalence of 26.7% in a meta-analysis of observational studies.[12] Another meta-analysis reported that colistin was associated with a significantly higher risk of nephrotoxicity than β-lactam-based regimens (relative risk, 2.40; 95% confidence interval [CI], 1.47–3.91).[13] Risk factors include advanced age, chronic comorbid conditions, hypoalbuminemia, and concomitant nephrotoxic agents.[10] The risk notably increases when the Css,avg value of colistin exceeds 2.5 mg/L, highlighting the importance of careful dosing and monitoring.[11]

Given this narrow therapeutic index, therapeutic drug monitoring has been increasingly recognized as essential for optimizing colistin therapy. Nonetheless, precise dosing remains challenging owing to the inter-individual variability in pharmacokinetics and insufficient population-specific data, particularly in Korean patients. Pharmacokinetic and safety data for CMS and colistin in Asian populations, including Koreans, remain scarce compared with those available for Western populations. Furthermore, because serum creatinine is a delayed marker of kidney injury, early biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, and kidney injury molecule-1 (KIM-1) have attracted considerable interest as potential predictors of colistin-induced nephrotoxicity; however, their clinical utility in relation to quantified colistin exposure has not been systematically evaluated. Thus, there is a critical knowledge gap regarding population-specific pharmacokinetic parameters and the early detection of colistin-induced kidney injury, which limits the ability to individualize therapy and to balance efficacy against nephrotoxicity in clinical practice.

In this context, applying a clinically recommended dosing regimen that reflects relevant exposure, together with the simultaneous measurement of nephrotoxicity biomarkers, would facilitate the characterization of the pharmacokinetics and renal safety of CMS under conditions that closely resemble real-world clinical practice. Such an approach may also help clarify how CMS and colistin pharmacokinetic profiles observed in Korean individuals relate to those reported in other ethnic and patient populations, offering insights into possible population differences in drug exposure and nephrotoxicity. Furthermore, characterizing the temporal profiles of early renal biomarkers alongside CMS and colistin exposure in healthy volunteers could lay the groundwork for developing exposure–biomarker relationships applicable to patients with increased renal risk, including those with pre-existing renal impairment, advanced age, or concomitant nephrotoxic therapies.

Therefore, to enable individualized and safe colistin therapy, it is crucial to establish population-specific pharmacokinetic parameters and validate early biomarkers of renal injury. Based on this rationale, this study was designed to evaluate the pharmacokinetics and renal safety of CMS following single and multiple intravenous administrations in healthy Korean male volunteers.

Materials and Methods

Subjects

Healthy male volunteers aged 19–45 years, with a body mass index (BMI) between 18.0 and 27.0 kg/m^2, were recruited for this study. The sample size was determined based on feasibility, reflecting the exploratory nature of this pharmacokinetic and renal safety evaluation in healthy volunteers. Prior to enrollment, all participants received a detailed explanation of the study procedures and voluntarily signed a written informed consent form. Screening for eligibility involved evaluation of medical history, physical examination, 12-lead electrocardiography, and standard clinical laboratory tests. The study protocol and informed consent documents were reviewed and approved by the Korean Ministry of Food and Drug Safety and the Institutional Review Board of Kyung Hee University Hospital (KHUH), Seoul, Republic of Korea (IRB number: KHUH 2019–11-060). The study was conducted in accordance with the Declaration of Helsinki and Korean Good Clinical Practice (Clinical Research Information Service, CRIS [https://cris.nih.go.kr]; registry number: KCT0005944).

Design

The study included a 4-day hospitalization period that lasted for 7–9 days, excluding the screening period. Subjects who passed the screening evaluation were admitted on the morning of Day −1 and discharged on the morning of Day 4. CMS was intravenously administered five times: twice daily on Days 1 and 2, and once on Day 3. Each dose consisted of 2.5 mg potency per kilogram of body weight (equivalent to 2.5 mg of colistin base activity), diluted in 50 mL of normal saline and infused over 1 h every 12 h (q12h) for 2.5 days.

To ensure safety, the maximum dose per administration of CMS was limited to 150 mg (equivalent to 150 mg of colistin base), corresponding to a maximum daily dose of 300 mg. This restriction was based on the maximum allowable daily dose approved by the Korean Ministry of Food and Drug Safety. Likewise, the European Medicines Agency specified a maximum maintenance dose of 300 mg CMS potency per day. In contrast, the US Food and Drug Administration has established a slightly higher maximum daily maintenance dose of 360 mg for CMS.

Pharmacokinetic Assessment

For the pharmacokinetic determination of CMS and colistin, blood samples were collected before the administration of each drug from Days 1 to 3. At the first and last administrations (on Days 1 and 3, respectively), blood samples were sequentially collected at 0.5, 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 8, 10, and 12 (immediately before the second dosing) h, and at 0.5, 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 14, 24 (Day 4, 0 h), 48 (Day 5, 0 h) h after the last dosing. Urine samples were collected before the first drug administration and at time intervals of 0–3, 3–6, 6–9 and 9–12 h after the first dose on Day 1 and at time intervals of 0–3, 3–6, 6–9, 9–12, and 12–24 h after the last dose on Day 3.

Renal Safety Assessments

Biomarkers of nephrotoxicity were evaluated in both blood and urine samples. Serum biomarkers included cystatin C and NGAL, while urinary biomarkers included clusterin, KIM-1, N-acetyl-β-D-glucosaminidase (NAG), and NGAL. Blood and urine samples were collected prior to the first dose on Day 1, before each subsequent dose, and at 12, 24 (Day 2, 0 h), 36, 48 (Day 3, 0 h), 60, 72 (Day 4, 0 h), and 96 (Day 5, 0 h) h after the last dose. Baseline values were defined as the pre-dose measurements obtained prior to the first dose (Day 1, 0 h). Changes from baseline were calculated for each participant at each post-baseline time point (ie, the value at each time point minus the baseline value).

Determination of Colistin Concentration

Colistin concentrations in plasma and urine were quantified using a previously validated liquid chromatography tandem mass spectrometry method.[14] The analysis was performed using a Waters® Acquity UPLC I-Class system coupled with a SCIEX 5500 Qtrap Plus mass spectrometer. Chromatographic separation was achieved on a Zorbax Eclipse C18 column (100 × 2.1 mm, 3.5 μm) maintained at 40°C. The mobile phase comprised 0.1% trifluoroacetic acid in water (solvent A) and acetonitrile (solvent B). Gradient elution was performed by increasing the proportion of solvent B from 10 to 80% over 3 min, followed by re-equilibration at 10%. Detection was performed in the positive ionization mode using multiple reaction monitoring (MRM), with a dwell time of 100 ms per transition. Data acquisition and processing were performed using Analyst® 1.7.1 and MultiQuant™ 3.0 software (SCIEX, Toronto, Canada).

For quantification, colistin concentration was calculated as the sum of colistin A and colistin B. Quantification was based on MRM transitions of m/z 585.6 → 101.1 for colistin A, 578.7 → 101.1 for colistin B, and 602.6 → 101.2 for polymyxin B1 (internal standard).

In plasma, the method demonstrated linearity over the range of 0.1–20 μg/mL (0.043– 8.61 μg/mL for colistin A and 0.057–11.39 μg/mL for colistin B), with correlation coefficients (r^2) ≥ 0.9970. The lower limits of quantification (LLOQ) were 0.043 μg/mL for colistin A and 0.057 μg/mL for colistin B. Intra- and inter-day precision (%CV) ranged from 1.26% to 7.99% and 2.49% to 8.00%, respectively. The corresponding accuracies (relative error, RE%) ranged from −4.20% to 7.75% and −4.75% to 14.80%, respectively.

When applied to urine samples, the method exhibited linearity over the range of 1–200 μg/mL (0.45–89.80 μg/mL for colistin A and 0.55–110.20 μg/mL for colistin B), with correlation coefficients (r^2) ≥ 0.9981. The LLOQs were 0.45 μg/mL for colistin A and 0.55 μg/mL for colistin B. Intra- and inter-day precision ranged from 1.45% to 6.82% and 2.01% to 7.65%, respectively, while accuracy ranged from −3.95% to 8.20% and −5.60% to 12.75%, respectively.

Pharmacokinetic Analysis

Pharmacokinetic parameters were calculated using the non-compartmental method with Phoenix™ WinNonlin® 8.3 (Certara USA Inc., Princeton, NJ, USA). The maximum concentration (C_{max}) and time to reach C_{max} (T_{max}) were obtained directly from the individual plasma concentration-time profiles. The terminal elimination rate constant (kz) was determined by linear regression of the log-transformed concentration-time data during the terminal phase. The terminal elimination half-life ($t_{1/2}$) was calculated as the natural logarithm of 2 divided by kz ($t_{1/2} = \ln(2)/kz$). The area under the plasma concentration-time curve (AUC) during the dosing interval (AUC_τ) was calculated using the linear/log trapezoidal rule. Total clearance (CL_{tot}) was defined as the ratio of intravenous dose to the AUC, representing the overall elimination of the administered drug from plasma via both renal excretion and conversion pathways, depending on the disposition characteristics of CMS or colistin. The accumulation index (R) was calculated as follows: $R_{Cmax} = C_{max}$(multiple) / C_{max}(single) and $R_{AUC0\text{-}12h} = AUC_{0\text{-}12h}$(multiple) / $AUC_{0\text{-}12h}$(single).

Urinary excretion data were calculated based on a previously reported non-compartmental analysis approach.[15] Renal clearance (CL_r) of colistin was preliminarily estimated using urine and plasma data collected during the 12–24 h after the last dose, during which CMS was considered to be almost eliminated. Renal clearance of CMS was estimated using urine and plasma data obtained during the 0–12 h after the last dose. This method allowed estimation of the actual amount of colistin excreted in each interval, and the unchanged amount of CMS excreted in urine was derived accordingly.[15] The fraction of CMS excreted unchanged in urine (f_e) was calculated as the ratio of renal to total clearance of CMS. Since CMS is either eliminated unchanged via the kidney or systemically converted to colistin, the fraction converted to colistin (f_m) was subsequently derived as $f_m = 1 - f_e$.

Safety and Tolerability Assessment

Safety and tolerability were evaluated throughout the study period by assessing adverse events (AEs), vital signs, 12-lead electrocardiogram, physical examinations, and clinical laboratory tests. All AEs were monitored, and their causal relationships to the study drug, CMS, were assessed by the investigators. Changes in clinical and laboratory parameters from baseline were also considered in the overall tolerability assessment.

Statistical Analysis

Continuous variables are presented as means with standard deviations (SD), and categorical variables are presented as frequencies and percentages. The estimated glomerular filtration rates (eGFR) were individually calculated using the Cockcroft–Gault equation, Modification of Diet in Renal Disease (MDRD) study equation, and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[16–18] The *p* values for changes in urinary recovery were calculated using paired t-tests or Wilcoxon signed-rank tests, depending on data normality, and for renal biomarkers, both absolute values and changes from baseline are presented as means and 95% confidence intervals (CIs) at each time point. All data were analyzed using SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA), and all figures were generated using the ggplot2 package in R software.[19,20]

Results

Demographic Characteristics

Twelve healthy male participants were enrolled in the study. The mean (SD, range) age, weight, height, and BMI of the 12 participants were 23.67 years (SD 3.42, range 20.00–31.00), 75.51 kg (8.61, 60.20~86.50), 175.95 cm (3.42, 171.20–181.40), and 24.37 kg/m^2 (2.40, 19.90–27.00), respectively. Baseline renal function parameters included a mean serum creatinine level of 0.92 mg/dL (SD 0.09, range 0.68~1.05) and eGFR calculated by different equations as follows: Cockcroft–Gault, 133.84 mL/min (24.70, 105.37–193.63); MDRD, 102.74 mL/min/1.73 m^2(16.31, 86.78–148.67); and CKD-EPI, 116.88 mL/min/1.73 m^2 (9.76, 101.65–136.47). One subject withdrew from the study before dosing on Day −1. The remaining 11 subjects completed the study and were included in pharmacokinetic and safety analyses.

Pharmacokinetic Characteristics

The plasma concentration-time profiles of CMS and colistin following repeated dosing are shown in Figure 1, and the pharmacokinetic parameters are listed in Table 1. After the initial 1-h intravenous infusion of CMS, the mean (SD) C_{max} was 34.03 (9.28) μg/mL, which was reached immediately post-infusion. The CMS levels declined rapidly, reaching a mean trough concentration of 0.43 (0.17) μg/mL immediately before the next scheduled dose at 12 h. For colistin, the mean C_{max} of 2.98 (1.07) μg/mL was attained approximately 2.5 h post-infusion, after which the plasma concentration decreased to 0.58 (0.22) μg/mL at 12 h.

CMS was administered five times at 12-h intervals. Following the final dose, the mean C_{max} of CMS and colistin were 32.76 (11.09) μg/mL and 4.18 (1.55) μg/mL, respectively. The T_{max} values were 1.0 and 1.5 h for CMS and colistin, respectively.

Repeated-dose pharmacokinetic evaluation indicated minimal CMS accumulation. The mean C_{max}, trough concentrations at 12 and 60 h (C_{12} and C_{60}), and $AUC_{0\text{-}12h}$ values on Days 1 and 3 were comparable. Specifically, the mean $AUC_{0\text{-}12h}$ values for CMS were 76.88 (20.86) μg·h/mL on Day 1 and 70.19 (24.16) μg·h/mL on Day 3, indicating negligible accumulation. In contrast, accumulation of colistin was observed. The mean AUC values increased from 18.53 (5.38) μg/mL on Day 1 to 25.63 (6.15) μg/mL on Day 3, suggesting accumulation with repeated dosing.

The elimination half-life displayed a similar pattern. The half-life of CMS remained relatively unchanged (2.26 h after the first dose versus 2.31 h on Day 3), whereas that of colistin exhibited a prolonged elimination half-life, increasing from 3.62 to 4.53 h. This trend was further supported by the accumulation indices of $AUC_{0\text{-}12h}$: 0.91 for CMS and 1.4 for colistin, indicating a notable accumulation of colistin compared with that of CMS over the course of repeated administration.

Urinary pharmacokinetic evaluation revealed distinct excretion patterns of CMS and colistin in Table 2 and Figure 2. The mean CL_r of CMS was 2.96 (3.15) L/h on Day 3, while that of colistin was lower, with a value of 0.30 (0.42) L/h. CMS showed predominant urinary recovery within the first 3 h post-dose, accounting for 28.6 (16.55) % of the administered dose on Day 1 and 43.13 (49.47) % on Day 3, with negligible recovery beyond 12 h. In contrast, urinary recovery of colistin was consistently low, with only 1–2% excreted within the first 3 h and approximately 3–5% recovered cumulatively over 12 h.

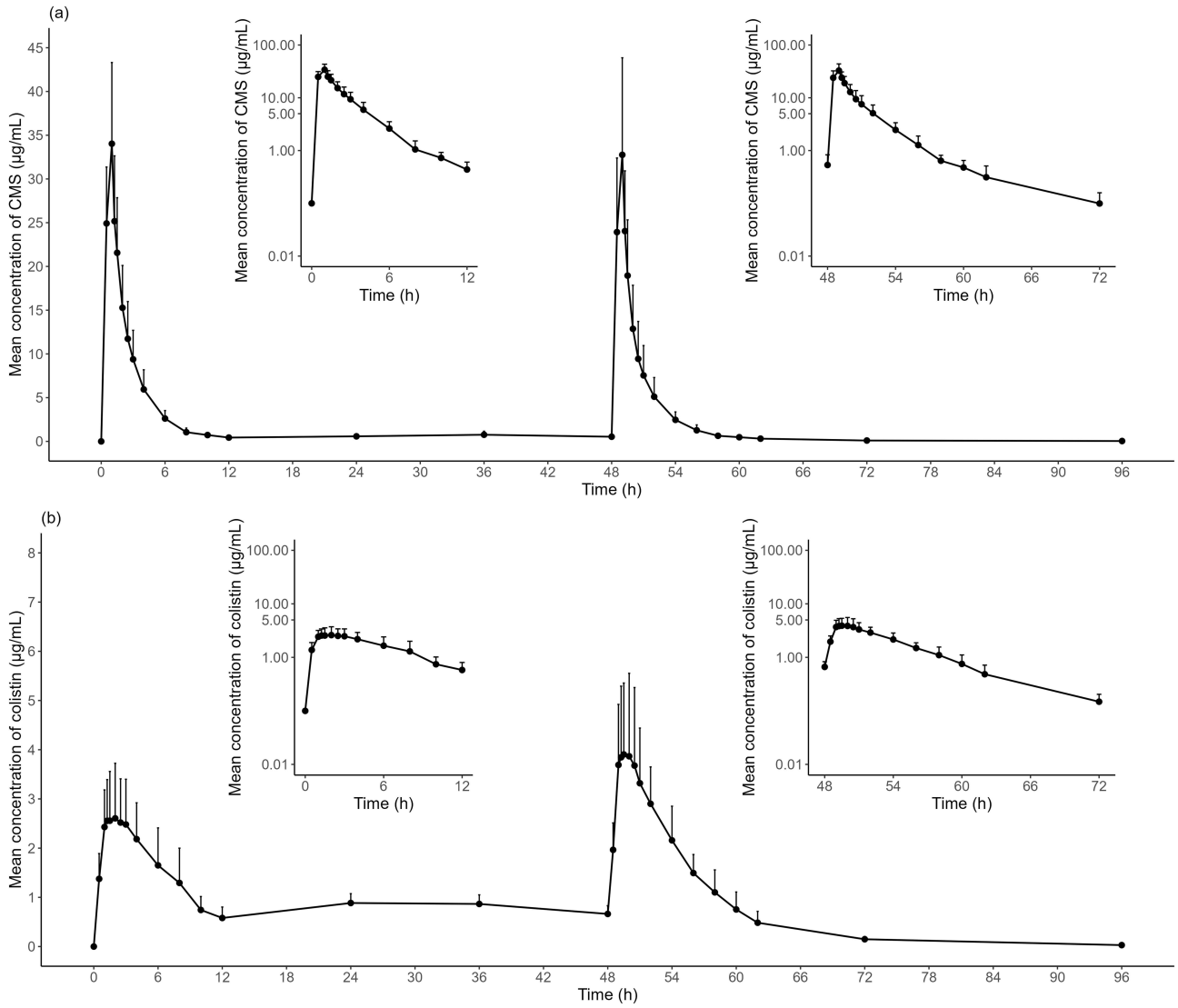

Figure 1 Mean plasma concentration-time profiles of (**a**) CMS and (**b**) colistin following multiple intravenous doses of CMS in healthy volunteers.
Notes: Error bars represent the standard deviation. Mean plasma concentrations are presented on both linear and logarithmic scales (insets).
Abbreviation: CMS, colistin methanesulfonate.

Biomarker Characteristics and Comparative Analysis with Previous Studies

The mean concentrations of serum and urinary biomarkers are presented in Figure 3, and detailed results are shown in Table 3 (Supplementary Table 1). The comparative data from previous studies are summarized in Table 4.

Serum biomarkers, including NGAL, cystatin C, blood urea nitrogen (BUN), and creatinine, were measured 12 h after each CMS administration and compared with baseline (pre-dose) levels. No consistent increase was observed relative to the baseline. Additionally, no delayed elevations were detected when biomarker levels measured at 12, 24, and 48 h after the final dose (ie, measurements at 60, 72, and 96 h) were compared with baseline levels. Although a slight increase in serum creatinine was noted at 36 h, the values remained within the normal reference range (0.5–1.8 mg/dL). One subject exhibited an elevated creatinine level (~1.9 mg/dL) at 96 h, the final time point. However, this returned to within the normal range at the safety follow-up visit (Day 8), and the elevation was deemed clinically non-significant.

Regarding urinary biomarkers, although one subject had a notably high value at the final time point, the overall trends were consistent with those observed for serum biomarkers. Group-level analysis of the mean and median values over time indicated urinary NAG and KIM-1 levels tended to increase at 96 h.

Table 1 Plasma Pharmacokinetic Parameters of CMS and Colistin Following Multiple Intravenous Doses of CMS in Healthy Volunteers

	CMS		**Colistin**	
	Day 1 (Single)	**Day 3 (Multiple)**	**Day 1 (Single)**	**Day 3 (Multiple)**
T_{max} (h)	1.02 (1.00–1.08)	1.00 (1.00–1.07)	2.5 (1.05–6.00)	1.5 (1.00–4.00)
C_{max} (μg/mL)	34.03±9.28	32.76±11.09	2.98±1.07	4.18±1.55
R_{Cmax}	0.96±0.19 (0.84,1.09)		1.42±0.26 (1.25,1.60)	
$AUC_{0\text{-}12h}$ (μg·h/mL)	76.88±20.86	70.19±24.16	18.53±5.38	25.63±6.15
$R_{AUC0\text{-}12h}$	0.91±0.17 (0.80,1.03)		1.40±0.12 (1.32,1.48)	
$AUC_{0\text{-}24h}$ (μg·h/mL)		72.51±25.12		29.60±6.88
AUC_{inf}	78.48±20.13	71.79±24.05	21.56±5.31	31.16±8.68
$t_{1/2,0–12h}$ (h)	2.26±1.16	2.31±0.47	3.62±1.22	4.53±2.07
$t_{1/2,0–24h}$ (h)		4.36±1.95		4.63±0.59
$CL_{tot,0–12h}$ (L/h)	4.89±1.37	5.49±1.67	7.31±1.62	5.10±1.26
$CL_{tot,0–24h}$ (L/h)		5.40±1.68		5.11 ± 1.15
f_m	0.62±0.20	0.59±0.24		
C_{0h}	0.00±0.00		0.00±0.00	
C_{12h}	0.43±0.17		0.58±0.22	
C_{24h}	0.58±0.29		0.88±0.19	
C_{36h}	0.76±0.41		0.87±0.19	
C_{48h}	0.53±0.30		0.66±0.17	
C_{60h}	0.48±0.17		0.75±0.35	
C_{72h}	0.09±0.05		0.16±0.03	
C_{96h}	NA		NA	

Notes: Values are presented as mean ± standard deviation (SD). For the accumulation index (R), 95% confidence intervals are shown in parentheses. An f_m value from one subject was excluded from the multiple-dose analysis due to an unreliable estimate caused by excessive urine volume. All concentrations at 96h (C_{96h}) were below the lower limit of quantification, and therefore mean±SD values were not calculated.
Abbreviations: CMS, colistin methanesulfonate; C_{max}, maximum plasma concentration; T_{max}, time to reach C_{max}; R, accumulation index; $AUC_{0\text{-}12h}$, area under the concentration-time curve from 0 to 12 h; $AUC_{0\text{-}24h}$, AUC from 0 to 24 h; AUC_{inf}, AUC from 0 to infinity; $t_{1/2}$, terminal elimination half-life; CL_{tot}, total clearance; f_m, the fraction of CMS converted into colistin; C, concentration; NA, not available.

Consistent with previous reports in healthy participants and patients, urinary NAG levels showed delayed elevation following repeated CMS administration (Table 4). While previous studies have documented elevated urinary NGAL levels during CMS therapy, significant elevations in the present study were observed only 12 h after the first and final doses (ie, at 24 and 60 h compared with the baseline). However, consistent increases in NGAL levels were not observed with each dose.

Safety Profiles and Tolerability

In all the subjects, safety and tolerability assessments, including vital signs, physical examinations, and clinical laboratory tests, revealed no clinically significant findings or notable changes from baseline. One patient experienced mild neck stiffness after abruptly rising from the bed on the day of discharge. The event was transient, resolved without intervention, and was assessed as unrelated to CMS.

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Table 2 Urinary Pharmacokinetic Parameters of CMS and Colistin Following Multiple Intravenous Doses of CMS in Healthy Volunteers

	CMS			Colistin		
	Day 1 (Single)	**Day 3 (Multiple)**	***p* value**	**Day 1 (Single)**	**Day 3 (Multiple)**	***p* value**
CL_R (L/h)		2.96±3.15			0.30±0.42	
Corrected fraction (mg)						
0–3 h	102.97±59.59	155.26±178.09		2.26±4.11	3.08±5.06	
3–6 h	23.75±12.77	32.47±19.02		1.78±2.59	2.47±3.63	
6–9 h	6.38±2.72	6.26±4.77		0.94±0.83	1.38±1.70	
9–12 h	2.48±1.90	2.54±2.07		0.48±0.42	0.67±0.49	
12–24 h		1.25±0.90			0.84±0.54	
Recovery (%)						
0–3 h	28.60±16.55	43.13±49.47	0.4131	1.51±2.74	2.05±3.37	0.0010
3–6 h	6.60±3.55	9.02±5.28	0.0986	1.18±1.72	1.65±2.42	0.0010
6–9 h	1.77±0.76	1.74±1.33	0.8986	0.63±0.56	0.92±1.13	0.0244
9±12 h	0.69±0.53	0.71±0.57	0.8594	0.32±0.28	0.44±0.33	0.0008
12–24 h		0.35±0.25			0.56±0.36	

Notes: Values are presented as mean ± standard deviation (SD). The *p* values were calculated using the paired *t*-test or Wilcoxon signed-rank test, depending on normality.
Abbreviations: CMS, colistin methanesulfonate; CL_R, renal clearance.

Discussion

The present clinical investigation characterized the pharmacokinetics, renal biomarker responses, and safety profile of repeated intravenous CMS administration in healthy male subjects. Pharmacokinetic analysis revealed that CMS exhibited predictable behavior with minimal accumulation across dosing intervals, whereas its active metabolite, colistin, showed progressive accumulation, as indicated by increased AUC values and a prolonged elimination half-life by Day 3. Serum renal biomarkers, including NGAL, cystatin C, BUN, and creatinine, remained largely within normal reference ranges throughout the study period, without consistent or clinically meaningful deviations from baseline. Although urinary biomarkers exhibited a similar pattern, modestly delayed elevations in urinary NAG and KIM-1 levels were noted at 96 h, suggesting a potential lagging renal tubular response. Overall, repeated CMS administration over 2.5 days in this small sample of healthy men was well tolerated, with no clinically significant AEs or laboratory abnormalities, thereby supporting its short-term safety in individuals with preserved renal function.

The observed accumulation of colistin, but not CMS, over the dosing period aligns with the findings of previous reports and reflects the known conversion kinetics of CMS to its active form.[25,26] This progressive increase in colistin exposure warrants careful consideration in the clinical setting, particularly in patients with impaired renal function. In the clinical context, where patients present with comorbidities known to predispose them to renal impairment, such as diabetes mellitus, the potential for colistin accumulation further underscores the need for therapeutic drug monitoring and individualized dosing strategies.[27,28] Careful adjustment of dosing regimens based on renal function and drug concentration measurements may be critical in minimizing nephrotoxic risk while maintaining therapeutic efficacy. Overall, these pharmacokinetic findings support the use of CMS dosing strategies that target clinically recommended colistin exposure in patients with normal renal function and highlight the need for dose reduction, extended dosing intervals, or more intensive therapeutic drug monitoring in patients with impaired renal function or critical illness.

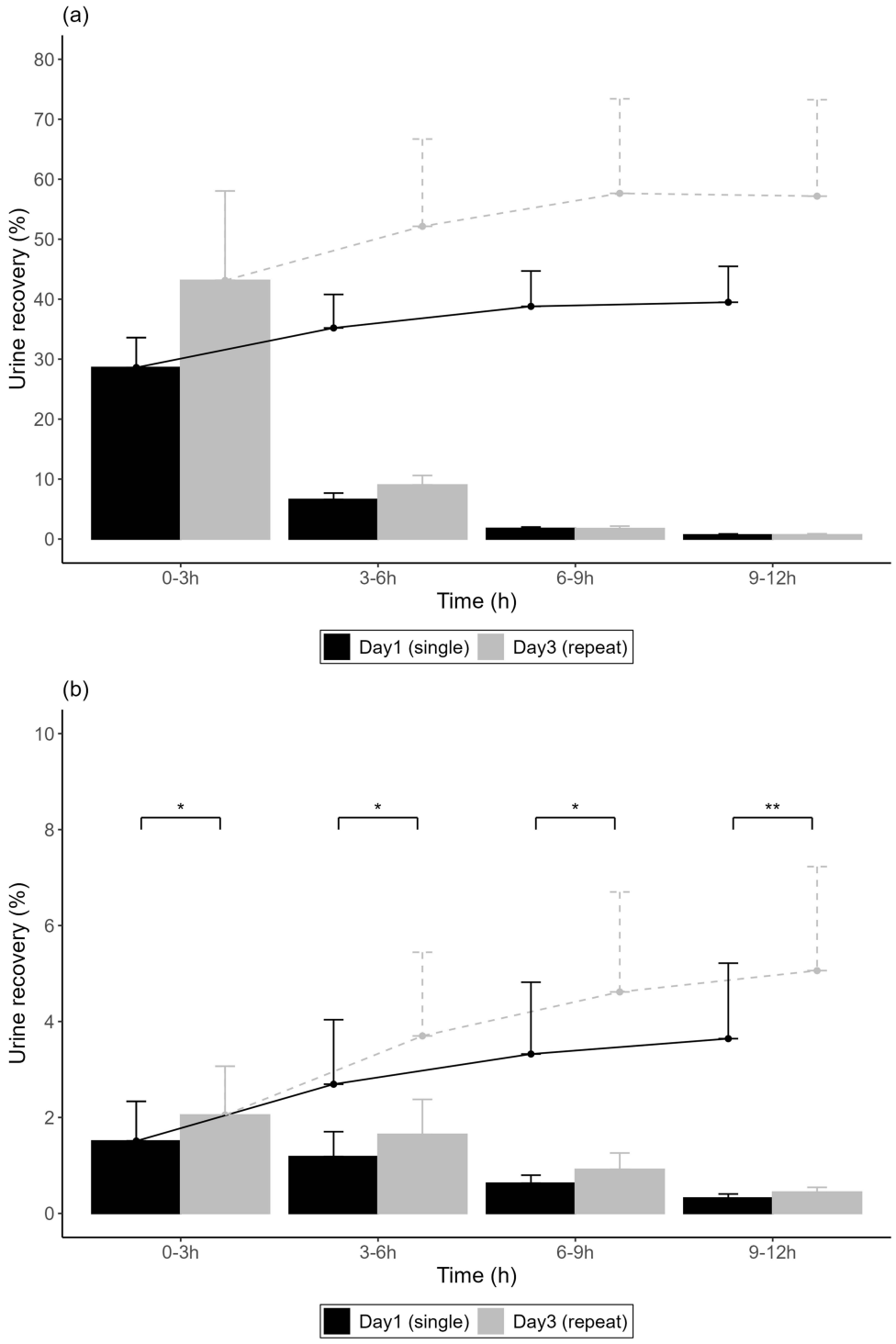

Figure 2 Mean and cumulative urinary recovery (%) of (**a**) CMS and (**b**) colistin following multiple intravenous doses of CMS in healthy volunteers.
Notes: Values are presented as mean ± standard deviation. $p < 0.05$ (*) $p < 0.01$ (**); tests based on normality (paired *t*-test or Wilcoxon signed-rank test).
Abbreviation: CMS, colistin methanesulfonate.

In the present study, we observed higher CMS plasma concentrations and AUC values than those reported previously, despite administration of a lower total CMS dose. For example, a previous study reported an $AUC_{0\text{-}12h}$ of 53.73 μg·h/mL following a 312-mg dose, while our study demonstrated greater systemic exposure with a dose of only 150 mg.[25] This discrepancy is likely due to differences in the hydrolysis conditions used for CMS quantification. Earlier studies typically

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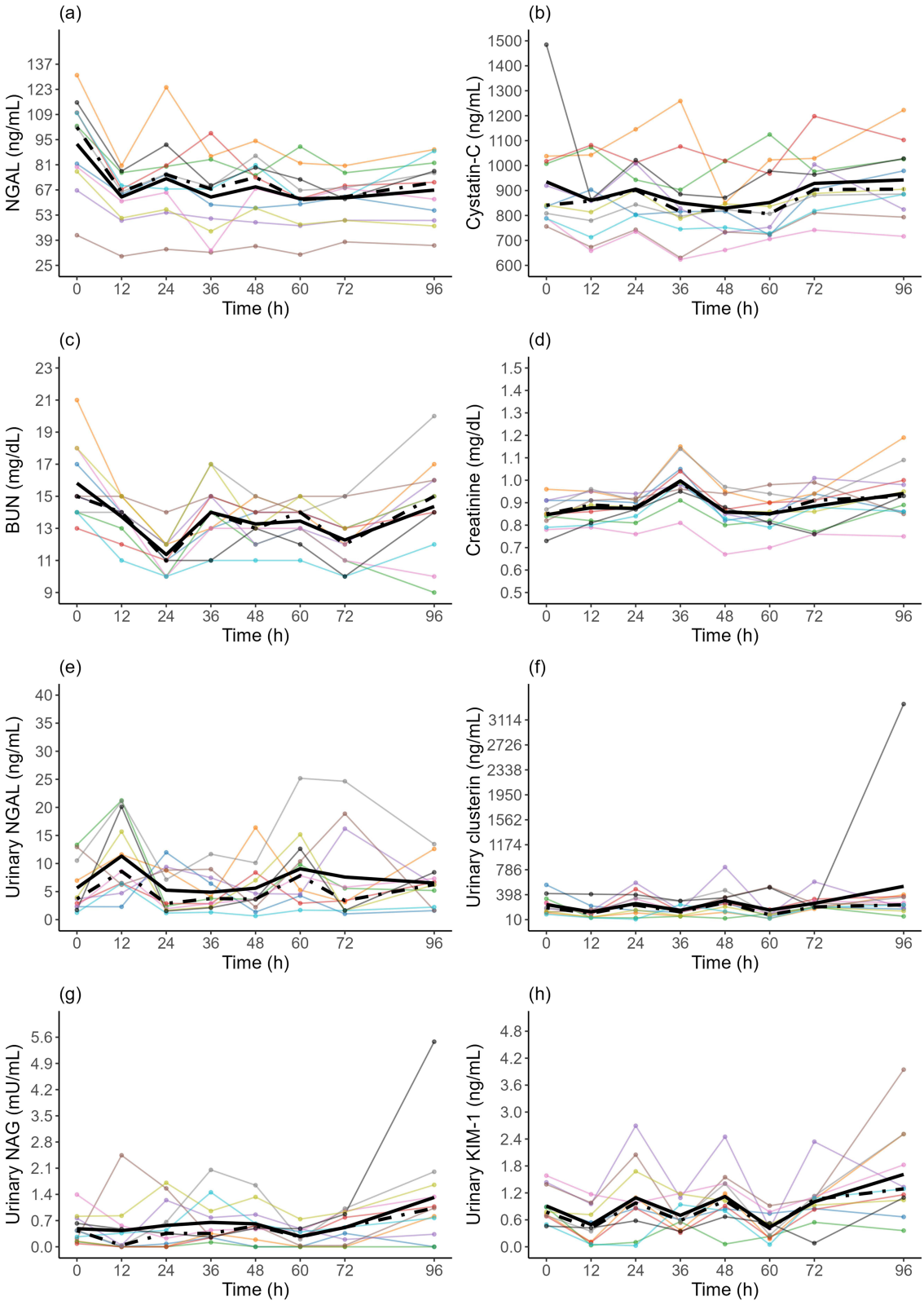

Figure 3 Changes in serum and urinary biomarker concentrations (**a-h**) following multiple intravenous doses of CMS in healthy volunteers.
Notes: Biomarker levels were measured at baseline and predefined time points after dosing. The bold line represents the mean, the dashed line represents the median, and the colored lines and points indicate individual values.
Abbreviation: CMS, colistin methanesulfonate; NGAL, neutrophil gelatinase-associated lipocalin; NAG, N-acetyl-β-D-glucosaminidase; KIM-1, kidney injury molecule-1.

Table 3 Changes in Renal Safety Biomarkers Following Multiple Intravenous Doses of CMS in Healthy Volunteers

Time	0 h	12 h	24 h	36 h	48 h	60 h	72 h	96 h
Serum								
NGAL (ng/mL)	92.55±25.61	63.09±14.74	73.27±23.11	63.04±21.61	68.71±17.45	62.05±16.67	62.61±12.39	66.89±17.96
Change		−29.46±12.70	−19.29±11.20	−29.52±14.43	−23.84±10.35	−30.50±14.89	−29.94±16.60	−25.66±10.87
Cystatin C (ng/mL)	935.00±208.39	860.00±153.49	905.38±132.20	850.08±184.75	829.34±112.69	851.82±146.46	928.64±125.44	942.5±146.63
Change		−75.01±192.99	−29.62±154.11	−84.93±200.00	−105.67±185.10	−83.19±157.93	−6.36±181.60	7.50±174.69
BUN (mg/dL)	15.82±2.40	13.73±1.27	11.36±1.21	14±2.05	13.27±1.27	13.45±1.21	12.27±1.74	14.36±3.14
Change		−2.09±1.87	−4.45±2.54	−1.82±3.28	−2.55±2.30	−2.36±2.34	−3.55±3.05	−1.45±3.72
Creatinine (mg/dL)	0.85±0.07	0.88±0.06	0.87±0.05	1.00±0.10	0.86±0.08	0.85±0.08	0.88±0.09	0.94±0.12
Change		0.03±0.04	0.03±0.06	0.15±0.07	0.01±0.09	0.00±0.08	0.04±0.07	0.09±0.10
Urine								
NGAL (ng/mL)	5.64±4.56	11.32±7.04	5.24±3.99	4.89±3.30	5.61±4.62	9.06±6.81	7.59±8.29	6.51±3.97
Change		5.69±6.64	−0.39±5.30	−0.75±3.81	−0.02±5.88	3.43±6.22	1.95±6.66	0.88±5.68
Clusterin (ng/mL)	244.26±142.78	130.97±108.84	260.23±184.12	155.38±87.32	304.58±212.31	160.01±179.17	263.33±121.11	527.92±945.30
Change		−113.29±115.58	15.98±224.07	−88.87±162.13	60.33±263.28	−84.25±214.04	19.08±199.28	283.66±903.31
NAG (mU/mL)	0.48±0.39	0.43±0.73	0.57±0.64	0.65 ± 0.61	0.61±0.51	0.28±0.25	0.52±0.41	1.32±1.52
Change		−0.05±0.81	0.09±0.67	0.17±0.70	0.13±0.56	−0.21±0.31	0.03±0.39	0.83±1.48
KIM-1 (ng/mL)	0.91±0.39	0.49±0.41	1.09±0.80	0.70±0.34	1.12±0.61	0.44±0.28	1.00±0.54	1.61±1.03
Change		−0.42±0.23	0.18±0.63	−0.21±0.37	0.21±0.48	−0.48±0.30	0.09±0.45	0.70±0.97

Notes: Values are presented as mean ± standard deviation (SD). Changes in values were expressed relative to baseline (0 h).
Abbreviations: CMS, colistin methanesulfonate; NGAL, neutrophil gelatinase-associated lipocalin; NAG, N-acetyl-β-D-glucosaminidase; KIM-1, kidney injury molecule-1.

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Table 4 Comparison of Renal Biomarkers Between the Present Study and Previous Reports

Serum	**Creatinine**			**NGAL**		
Time(h)	**Present study (mg/dL)**	**Shabani et al[21] (mg/dL)**	**Ordooei Javan et al[22] (mg/dL)**	**Present study (ng/mL)**	**Ordooei Javan et al[22] (pg/mL)**	**Ordooei Javan et al[22] (pg/mL) [AKI group]**
0	0.85±0.07	1.14±1.70	0.90±0.20	92.55±25.61	620.7±296.1	569.1±259.2
12	0.88±0.06			63.09±14.74		
24	0.87±0.05	0.95±0.54		73.27±23.11		
36	1.00±0.10			63.04±21.61		
48	0.86±0.08	1.06±0.72	1.00±0.32	68.71±17.45	659.4±324.1	609.8±294.1
60	0.85±0.08			62.05±16.67		
72	0.88±0.09	1.16±0.93		62.61±12.39		
96	0.94±0.12	1.27±0.89	1.20±0.57	66.89±17.96	683.2±340.3	704.9±273.5
120		1.42±0.97				
Day 7 or 8	0.93±0.11		1.40±0.77		764.6±361.7	874.3±292.6
Day 10			1.77±1.00		762.1±415.4	884.0±330.4
Urine	**NAG**			**NGAL**		
Time (h)	**Present study (mU/mL)**	**Mizuyachi et al[23] (IU/g creatinine)**		**Present study (ng/mL)**	**Sirijatuphat et al[24] (μg/h)**	**Sirijatuphat et al[24] (μg/h) [AKI group]**
0	0.48±0.39	1.14±0.73		5.64±4.56	32.6±32.1	31.6±24.6
12	0.43±0.73	0.63±0.18		11.32±7.04		
24	0.57±0.64	0.86±0.57		5.24±3.99		
36	0.65±0.61	2.62±3.34		4.89±3.3		
48	0.61±0.51	4.03±5.03		5.61±4.62	66.2±55.1	56.3±51.7
60	0.28±0.25	3.04±2.77		9.06±6.81		
72	0.52±0.41	2.74±1.71		7.59±8.29		
84		3.50±6.71				
96 or ET	1.32±1.52	1.95±1.15		6.51±3.97	74.5±60.2	52.3±50.9

Notes: Values are presented as mean ± standard deviation (SD).
Abbreviations: NGAL, neutrophil gelatinase-associated lipocalin; NAG, N-acetyl-β-D-glucosaminidase; AKI, acute kidney injury ; ET, end of treatment.

employed sulfuric acid-mediated hydrolysis at room temperature (eg, 0.5 M H_2SO_4 for 15–30 min), assuming complete conversion of CMS to colistin.[23,25,29] However, a previous study indicated that these conditions may result in incomplete hydrolysis, leading to an underestimation of CMS concentrations.[30] The authors showed that complete conversion was achieved only under more stringent conditions, specifically, treatment with 0.5 M sulfuric acid at 60°C for 10 min. Based on this evidence, we adopted a heat-assisted hydrolysis protocol using formic acid at 60°C, which likely facilitated more efficient conversion of CMS to colistin and yielded more accurate quantification results.

To support this interpretation, we performed a comparative analysis of AUC values from previous studies and those obtained in our study (see Supplementary Table 2). Despite the lower administered dose, our AUC values were consistently higher than those reported previously, supporting the notion that our hydrolysis method accurately reflects

true CMS exposure. These findings highlight the critical importance of using rigorously validated hydrolysis protocols to ensure accurate pharmacokinetic evaluation of CMS.

In this study, we evaluated changes in serum and urinary biomarkers following repeated CMS administration in healthy subjects. Compared with baseline values, no consistent elevations were observed in key serum nephrotoxic biomarkers, including NGAL, cystatin C, BUN, and creatinine. Although transient increases in serum creatinine levels were detected at certain time points, these values remained within normal reference ranges. Among the urinary biomarkers, urinary NGAL increased only at early time points but did not show consistent elevations throughout the dosing period. A similar increase in urinary NGAL following colistin administration was reported in a study involving patients with pneumonia or tracheobronchitis caused by MDR Gram-negative bacteria.[24] Urinary NAG and KIM-1 tended to show delayed elevation after repeated CMS exposure at 96 h post-administration. A study in healthy Japanese volunteers similarly reported a transient increase in urinary NAG after colistin administration, followed by recovery.[23] Although slight elevations in NGAL were observed at earlier time points and in NAG and KIM-1 at later time points, the overall biomarker profiles did not suggest clinically significant nephrotoxicity. These subtle trends may reflect early subclinical tubular stress; however, their clinical relevance remains uncertain in the context of preserved renal function.[31–33] Moreover, these results reinforce the need for monitoring multiple biomarkers and cautious interpretation in early-phase nephrotoxicity studies.

These findings highlight the inherent limitations of biomarker-based nephrotoxicity assessment in healthy individuals. In subjects with normal renal function, CMS-induced kidney injury is likely to be minimal or transient, leading to biomarker fluctuations that frequently remain within the normal reference ranges, consistent with previous reports in healthy volunteers.[23,26] Such variations may reflect physiological variability rather than clinically meaningful toxicity, thereby limiting the sensitivity and specificity of these biomarkers in detecting true renal injury in healthy individuals. Therefore, caution should be exercised when extrapolating these results to clinical settings involving patients with predisposing risk factors for renal impairment. Future studies should prioritize populations with greater susceptibility to kidney injury to elucidate biomarker kinetics more clearly and characterize differences in the extent and pattern of changes compared with healthy controls. Incorporating a panel of complementary biomarkers and aligning biomarker dynamics with clinical endpoints may enhance the diagnostic utility of biomarker-guided nephrotoxicity monitoring.

The primary limitation of the current study is the inclusion of healthy individuals with intact renal function, which may not fully reflect the nephrotoxic responses observed in clinical populations. Furthermore, the short exposure period of 2.5 days may be insufficient to capture delayed biomarker responses and limits definitive conclusions regarding potential cumulative or long-term nephrotoxic effects. Additionally, the relatively small sample size (n=11) limits the statistical power and generalizability of the findings. This study did not evaluate urinary proteins, serum electrolytes, oxidative stress markers, or inflammatory markers, which further limits the comprehensiveness of the renal safety assessment. The evaluation of a single CMS dosing regimen in a homogeneous group of young Korean men further constrains the external generalizability of the results and precludes the assessment of relative nephrotoxicity.

Notably, our findings suggest that the CMS concentrations may have been underestimated in previous pharmacokinetic studies involving both healthy subjects and patients. This underscores the importance of cautiously interpreting concentration-to-dose relationships in future pharmacokinetic evaluations of colistin. Although the current results support the short-term safety of CMS in healthy individuals, they should be regarded as hypothesis-generating and supportive, rather than definitive evidence of renal safety. Further studies in patients at an increased risk of renal impairment are needed to determine whether similar safety profiles are maintained under real-world clinical conditions. Continued investigation in vulnerable populations, along with careful pharmacokinetic evaluation and longitudinal multiple biomarker monitoring, is essential to optimize the safe and effective use of colistin-based therapies.

Conclusion

In conclusion, repeated intravenous administration of CMS in healthy subjects with normal renal function was well tolerated, with negligible nephrotoxic signals. CMS displayed predictable pharmacokinetics without substantial accumulation, whereas colistin showed progressive accumulation, emphasizing the importance of validated quantification methods and careful dosing in patients at renal risk. These findings should be interpreted with caution because of the

small sample size and limited study duration. Overall, the present findings provide preliminary data on short-term safety and biomarker responses to CMS in healthy individuals; however, larger, longer-term studies in patient populations are required to validate renal safety and confirm the clinical utility of early renal biomarkers.

Data Sharing Statement

The data can be made available upon request from the corresponding author.

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Disclosure

The authors declare that they have no competing interests.

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