Colistin methanesulphonate (CMS) and Colistin Pharmacokinetics in Critically Ill Patients Receiving Continuous Veno-venous Hemodiafiltration (CVVHDF)

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Running title: Colistin pharmacokinetics in CVVHDF
Abstract

This study describes the pharmacokinetics of colistin methanesulphonate and colistin in five intensive care unit patients receiving continuous veno-venous hemodiafiltration. For CMS, the mean \( C_{\text{max}} \) after fourth dose was 6.92 mg/L and total CL 8.23 L/h. For colistin, the mean concentration was 0.92 mg/L and CL/fm 18.91 L/h. Colistin concentrations were below the current MIC breakpoints, and \( fAUC/MIC \) was lower than recommended, suggesting that a dosage regimen of 160 mg CMS q8h is inadequate.
The use of colistin, an old antibiotic, has recently reemerged due to the increased prevalence of infections caused by multidrug-resistant Gram negative bacteria (MDR-GNB), especially in critically ill patients (4, 9). Such patients often suffer from acute renal impairment necessitating renal replacement therapy (15). However, there are only scarce data on the effect of renal replacement methods on the pharmacokinetics of colistin (5, 10-12). The present study was undertaken to study the elimination of CMS and colistin in patients undergoing CVVHDF to contribute to the knowledge regarding the pharmacokinetics of colistin in this population.

Patients admitted to the Critical Care Unit of University General Hospital “Attikon” in Athens, Greece, were eligible for the study if they fulfilled the following inclusion criteria: 1) age 18 years or older, 2) colistin treatment as part of their standard care due to probable or documented infection by MDR-GNB and 3) receiving CVVHDF as renal replacement therapy.

For each patient the following were recorded: age, body weight, serum creatinine, serum albumin, hemoglobin, hematocrit (Hct) and APACHE II score on the first day of colistin administration.

The study was approved by the Ethics Committee of the Hospital (Reg. No. 3/30-3-07). Informed consent was provided by the patients or nearest relatives.

CMS (Colistin, Norma, Greece) was administered according to local practice at a dose of 2 million units (MU), equivalent to 160 mg, dissolved in 100 ml of normal saline every 8 hours by intravenous infusion over 15 minutes.

Vascular access was obtained by insertion of a double lumen dialysis catheter. Each patient was dialysed using the Prisma system (Hospal-Gambro). Continuous venovenous hemodiafiltration (CVVHDF) was performed using an acrylonitrile and sodium methallyl sulfonate copolymer hollow fiber high-flux hemofilter (AN69 HF) with a membrane surface.
area of 0.9 m² (M100 predilution filter set, Hospal). Hemosol B0 solution (Gambro) was infused as substitution and dialysate fluid. The blood flow rate was set at 120-150 mL/min, filtration rate at 0.6-0.9 L/h and dialysate fluid rate at 1.5-2.5 L/h.

Venous blood was collected immediately before the first and fourth infusion and at 15, 30, 60, 90, 120, 180, 240 and 360 minutes after the end of the first and fourth infusion. Prefilter and postfilter blood samples were also collected immediately before and at 60, 120 and 360 minutes after the end of the fourth infusion. All blood samples were immediately refrigerated and centrifuged, and plasma was collected and stored at -70°C until assayed.

Concentrations of colistin A and B in plasma were determined by Liquid Chromatography tandem Mass Spectrometry (LC-MS/MS) (7, 14). Plasma concentrations of CMS were determined by hydrolysis of CMS to colistin using the method described by Li et al. (8) with modifications (14). The inter-day CV and accuracy for colistin was <4.4 % and <±1.9 %, and for CMS inter-day CV and accuracy was <8.2 % and <±3.2 %.

Total clearance was calculated, based on plasma concentrations, as $\text{CL}_{\text{tot}}=\frac{\text{Dose}}{\text{AUC}_{0-8h}}$, assuming steady state was achieved and extrapolation to 8 hours from the three last observations, after omission of apparent outliers. For colistin, the fraction metabolized ($f_{\text{m}}$) is undefined in this study, and clearance is therefore expressed as $\text{CL}_{\text{tot}}/f_{\text{m}}$, ($\text{CL}_{\text{tot}}/f_{\text{m}}=\frac{\text{Dose}}{\text{AUC}_{0-8h, \text{colistin}}}$ in molar terms). Dialyzer extraction ratio was calculated as $E=(C_{\text{in}}-C_{\text{out}})/C_{\text{in}}$, where $C_{\text{in}}$ and $C_{\text{out}}$ are the total plasma concentrations before and after filtering, and dialyzer clearance as $\text{CL}_{\text{HDF}}=E*Q*(1-Hct)$, where $Q$ is blood flow rate through the filter. Creatinine clearance was estimated with the Cockroft-Gault equation.

Five patients (3 female) of ages 57 – 83 years with a mean Apache II score of 18 (range 15 – 24) were included (Table 1). Concentration data from the first dose was available only
from two patients where CMS $C_{\text{max}}$ was 4.89 and 8.90 mg/L and $T_{\text{max}}$ was 0.75 and 0.5 h, respectively. Colistin $C_{\text{max}}$ was 0.18 and 0.40 mg/L and $T_{\text{max}}$ was the last observed time point, 6 h (figure 1).

After the fourth dose, $C_{\text{max}}$ for CMS was $6.92 \pm 2.83$ mg/L (mean ± SD), $T_{\text{max}}$ was 0.5 h and $C_{\text{min}}$ was $1.51 \pm 0.56$ mg/L (figure 2a). $CL_{\text{tot}}$ was $8.23 \pm 3.07$ L/h and the terminal half-life was 3.3 h. $E$ was $0.30 \pm 0.13$ (mean ± SD) (figure 3a), and $CL_{\text{HDF}}$ was 1.94 ± 0.80 L/h.

For colistin, concentrations remained at a plateau over the dosage interval with a concentration of $0.92 \pm 0.46$ mg/L (mean ± SD) (figure 2b). $CL_{\text{tot}}/f_m$ was $18.91 \pm 5.95$ L/h. $E$ was $0.68 \pm 0.08$ (mean ± SD) (figure 3b), and the corresponding $CL_{\text{HDF}}$ was $4.33 \pm 1.31$ L/h.

The present study describes the pharmacokinetics of CMS and its active metabolite colistin in critically ill patients receiving CVVHDF. The results are on par with previously published results by other investigators (5), showing that both CMS and colistin are eliminated with this technique. The dialyzer clearance was similar to the four patients on continuous renal replacement therapy reported by Garonzik et al (5), whereas Marchand et al (11) presented similar dialyzer extraction ratios. Unfortunately, colistin is notorious for its ability to be adsorbed to many different materials, such as laboratory utensils (Karvanen et al, poster D-690, 51st ICAAC, Chicago, IL) as well as HDF filters (12). Therefore, we were not able to reliably measure the concentrations of CMS and colistin in the combined dialysate/ultrafiltrate, and thus sieving was not possible to calculate.

The current opinion on the pharmacokinetics of colistin is that a main fraction ($f_e$) of the inactive CMS is mainly cleared renally, with a fraction being metabolized into the active substance colistin ($f_m$) (9). In healthy volunteers, $f_e$ has been determined to be 70%, and
assuming that $f_m = 1 - f_e$, $f_m$ is 30% (2). Colistin in turn is not eliminated renally, but is probably
eliminated by hydrolysis, although the mechanism of hydrolysis is not known. In patients with
renal failure, it is hypothesized that as the renal elimination of CMS is slower, $f_m$ will increase,
and thus increase the accumulation of colistin. This in turn suggests that total daily doses should
be lowered in these patients. However, when renal replacement therapy is introduced, it should
theoretically compensate for the decrease in renal clearance and thus reverse $f_m$ to normal
values. However, if the renal replacement therapy also eliminates colistin, as this and other
studies (5, 10-12) indicate, the achieved concentrations of colistin will be lowered. In
accordance with this, we found that the total clearance of CMS in our patients was similar to
what has been found in other reports (2, 5), except the studies by Plachouras et al (14) and
Mohamed et al (13), where the observed CL of CMS is higher. However, the pharmacokinetic
analyses in these two studies were performed using molar units, i.e. one molecule of
administered CMS can form one molecule of colistin. If the difference in molecular weight
between CMS and colistin had not been considered, CL values for CMS similar to those
estimated by Couet et al (2) and Garonzik et al (5) would have been obtained. Assuming that $f_m$
is 30% in all subjects, both patients and healthy volunteers, total CL of colistin would be
comparable between studies, with the exception of the current study, where the total CL of
colistin is calculated to be approximately the double value (5.7 L/h).

Comparing the found concentrations of colistin with the susceptibility breakpoints
defined by the European Committee on Antimicrobial Susceptibility Testing (3), the plasma
concentrations were roughly half of the breakpoint concentration for Acinetobacter spp. ($S \leq 2$
mg/L) and ¼ of the breakpoint concentration for Pseudomonas spp. ($S \leq 4$ mg/L). In addition,
Bergen et al (1) conclude that in order to reach a 2 log$_{10}$ killing target in animal models, the
fAUC/MIC of colistin should be in a range of 27.6-45.9. In this study, assuming that \( f_u \) is 34\% (13), the resulting mean fAUC/MIC for susceptible *Acinetobacter* and *Pseudomonas* species at the breakpoint MICs are 3.1 and 1.6, respectively. Conversely, the exposure profile from this study would exceed the recommended target only for bacteria with MICs equal to or lower than 0.12 mg/L.

In conclusion, both CMS and colistin are cleared by CVVHDF although the clearance of CMS is not restored to the values found in related studies (13, 14), and the data from this study corroborates findings in previous studies (5, 10-12). The used dosage regimen of 160 mg CMS q8h has been motivated by the risk of accumulation of drug and concomitantly increased risk of toxicity. However, this regimen together with the increased clearance of colistin results in colistin concentrations that are approximately half of the corresponding concentrations in patients without CVVHDF given 240 mg CMS q8h (14). The resulting drug exposure raises serious concerns regarding the optimal dosage and the need of dosage adjustment in patients receiving CVVHDF. On the basis of this study, we recommend that CMS dosage should not be reduced for patients undergoing CVVHDF but rather to be equal to or even higher than the daily dose in patients with normal renal function.

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References


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Table 1. Patient characteristics.

Figure 1. Concentrations of CMS and colistin after first dose in two patients.

Figure 2. Concentrations of CMS (a) and colistin (b) after fourth dose.

Figure 3. Median prefilter (C_in) and postfilter (C_out) concentrations of CMS (a) and colistin (b) after fourth dose.