Colistin pharmacokinetics in intensive care unit patients on continuous venovenous haemodiafiltration: an observational study

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Objectives: Available data on colistin pharmacokinetics in patients undergoing continuous renal replacement therapy (CRRT) are limited. Our aim was to study colistin pharmacokinetics in critically ill patients treated with colistin methane sulphonate for Gram-negative sepsis and undergoing continuous venovenous haemodiafiltration for acute renal failure.

Patients and methods: Three patients were studied. The colistin methane sulphonate dose administered was at the discretion of the attending physician and was in all cases lower than that recommended for individuals with intact renal function. Colistin methane sulphonate was administered intravenously over 30 min, and blood samples were collected from each patient pre- and post-filter for the HPLC determination of colistin levels in serum before infusion, at 10, 60, 120, 240, 360, 480 and 600 min from the end of infusion, and immediately before the next dose. Concurrently, spot samples of effluent from the haemofilter were also collected and analysed. Both colistin total extracorporeal clearance and clearance in the effluent were calculated.

Results: Extracorporeal clearance resulted in substantial removal of colistin (43%–59% of total colistin clearance). Total colistin clearance was found to be reduced (varying between 3.3 and 4.5 L/h), compared with patients with normal renal function. Colistin methane sulphonate dosage resulted in clearly suboptimal colistin steady-state concentrations.

Conclusions: In spite of substantial extracorporeal clearance, total colistin clearance was reduced, compared with patients with normal renal function. Colistin adsorption by the haemofilter contributed to its extracorporeal clearance to a large extent. Studies on other patients receiving colistin methane sulphonate and undergoing CRRT are required before more appropriate dosage regimens can be recommended.

Keywords: critical care, renal replacement therapy, colistin concentrations, extracorporeal clearance

Introduction

In the last decade, colistin has re-emerged as one of the few remaining treatment options for serious infections from multiresistant Gram-negative bacilli. Yet data on colistin pharmacokinetics in patients undergoing continuous renal replacement therapy (CRRT) are limited. Li et al.1 reported a patient undergoing continuous venovenous haemodiafiltration (CVVHF) and, more recently, a report was published in abstract form of five critically ill patients undergoing CVVHF.2 The large multicentre study of Garonzik et al.3 on the population pharmacokinetics of colistin methane sulphonate and colistin in critically ill patients includes some data on three patients undergoing continuous venovenous haemodialysis (CVVHD) and one patient undergoing continuous venovenous haemofiltration (CVVH). There is general agreement that a substantial proportion of colistin (which is the active drug, colistin methane sulphonate being only an inactive prodrug4) undergoes extracorporeal clearance and that current recommendations for colistin methane sulphonate dosing in patients undergoing CRRT should be revised upwards,1–3 although only Garonzik et al.3 go as far as to make tentative proposals for colistin methane sulphonate dosing in this setting. Our aim was to measure colistin levels and study colistin extracorporeal clearance in three critically ill patients undergoing CVVHDF following intravenous (iv) administration of colistin methane sulphonate.

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Patients and methods

Colistin levels in serum and colistin elimination with post-dilution CVVHDF (Baxter Accura system) were studied in three critically ill patients with acute renal failure (ARF), treated with colistin methane sulphonate for Gram-negative sepsis. The study was approved by the Hospital Ethics and Research Committee and performed in accordance with Good Clinical Practice guidelines. Informed consent was waived.

Patient 1 was a 45-year-old male multitrauma patient who developed ARF shortly after presentation, because of myoglobinuria. From day 4 of intensive care unit (ICU) stay, the patient was started on CVVHDF, while on day 5 colistin methane sulphonate treatment was initiated for ventilator-associated pneumonia due to Acinetobacter baumannii. Colistin sampling was performed on the third day of colistin methane sulphonate treatment. The patient exhibited neither clinical nor bacteriological response and died a few days later.

Patient 2 was a 62-year-old male diabetic with septic arthritis, who developed ARF and had to be treated with CVVHDF. While on CVVHDF the patient developed septic shock because of a bloodstream infection (BSI) from A. baumannii, and was treated with meropenem and colistin methane sulphonate. Colistin sampling was performed on day 10 of treatment. The A. baumannii infection was successfully treated. The patient died in the ICU 3 months later from other complications.

Patient 3 was a 58-year-old male multitrauma patient who developed ARF because of myoglobinuria and was in need of CVVHDF. On day 3 of CVVHDF the patient developed a BSI from A. baumannii and was started on colistin methane sulphonate. On days 2 and 3 of colistin methane sulphonate treatment the patient was taken off CRRT, but had to be restarted on day 4 as he became anuric. Colistin sampling was performed on day 6. There was a clinical and bacteriological response to treatment, but the patient died from other complications in the ICU, 20 days later.

In the three patients, the dosing regimen for colistin before and during CVVHDF was at the discretion of the attending physician. CVVHDF was performed using a hollow fibre haemofilter (Renaflo II Hemofilter HF 700, membrane area 0.71 m²).

Colistin methane sulphonate was administered iv over 30 min and blood samples were collected from each patient pre- and post-filter for the determination of colistin levels in serum, at the following timepoints: before infusion, at 10, 60, 120, 240, 360, 480 and 600 min from the end of infusion, and immediately before the next dose. Concurrently, spot samples of effluent from the haemofilter were collected. Handling of samples was as described previously.

Concentrations of colistin (i.e. colistin base) in serum and effluent were measured by an isocratic HPLC assay as previously reported. The intra- and interday variability was ≤6.3% and ≤8.0% for serum, and ≤6.3% and ≤9.2% for effluent, respectively. The lower limits of detection and quantification were 50 and 80 ng/mL for serum, and 16 and 53 ng/mL for effluent, respectively (calibration range for serum 300–3000 ng/mL and for effluent 100–1500 ng/mL).

The pharmacokinetic parameters of colistin in serum were estimated from the concentration–time data of each patient by non-compartmental analysis using the WinNonlin pharmacokinetic software package (Pharsight Corporation, Mountain View, CA, USA). For pharmacokinetic evaluations, the colistin methane sulphonate dose was corrected to an equivalent dose of colistin according to the molecular weight of the two major components, i.e. colistin methane sulphonate dose × 1163/1743 = colistin methane sulphonate dose × 0.667, where 1163 is the average molecular weight of colistin A and B, and 1743 is the average molecular weight of the respective sodium methane sulphonate salts. Since the precise percentage of colistin A and B in the batch of colistin methane sulphonate administered was unknown, the precise dose of the colistin base could not be estimated with greater accuracy.

The maximum concentration (Cmax) reflects the colistin serum concentration measured at 10 min from the end of infusion. The average concentration at steady state (Csteady) was calculated as AUC/τ, where AUC represents the area under the serum concentration–time curve, calculated by the linear trapezoidal method from the time of initiation of infusion to the time of the last observation, and τ represents the dosage interval. The elimination half-life (t1/2) was calculated as ln2/λ2, where λ2 (the elimination rate constant) was estimated by log-linear regression of the terminal portion of the serum concentration–versus-time curve (based on the last three data points). Approximate estimations for total clearance (CLapp) were computed as follows: CLapp = dose/AUC0–t or AC0–t.18

As regards clearance of colistin by the haemofilter, we calculated both the total extracorporeal clearance and clearance in the effluent. The difference between the two values (if any) is generally considered to represent drug adsorption by the haemofilter. In previous reports, only effluent and not total haemofilter clearance has been estimated.

Extracorporeal clearance (CLEC) was calculated as 

\[ C_{\text{EC}} = \frac{Q_{\text{b}}(1 - H_t)(C_{\text{n}} - C_{\text{app}})}{C_{\text{in}}} \]

where Qb corresponds to blood flow through the haemofilter, Ht to the haematocrit, and Cn and Capp correspond to the pre- and post-haemofilter serum concentrations, respectively.

An extraction ratio, or sieving coefficient (Ssc), was estimated as 

\[ S_{\text{sc}} = \frac{C_{\text{in}}}{C_{\text{in}} - C_{\text{app}}} \]

where Capp corresponds to the colistin concentration in spot effluent samples collected during each sampling interval, and Cn and Capp correspond to the pre- and post-haemofilter serum concentrations for the same sampling intervals, respectively. Effluent clearance (CLCVVHDF) was then calculated from Sc and the effluent flow rate (Q): 

\[ C_{\text{CVVHDF}} = S_{\text{sc}} \times Q \]

The fraction of extracorporeal clearance corresponding to effluent clearance was calculated as \( C_{\text{CVVHDF}}/C_{\text{EC}} \) and the fraction of extracorporeal clearance corresponding to total (apparent) clearance (CLapp) as \( C_{\text{EC}}/C_{\text{app}} \).

Results and discussion

Data on the colistin methane sulphonate dose, effluent flow rate and colistin elimination are presented in Table 1. Colistin concentrations achieved in the serum and effluent samples of each patient are shown in Figure 1.

In our patients, extracorporeal clearance resulted in substantial removal of colistin (43%–59% of total colistin clearance). Interestingly, only a fraction of colistin extracorporeal clearance could be attributed to dialfiltration. The difference between the effluent and total CVVHDF clearance probably represents the extent of membrane adsorption of colistin, which, besides removal by diffusion and convection in the effluent, appears to be important.

The extent of effluent clearance in our patients was very similar to that reported by Li et al. Yet, other investigators have reported higher effluent clearances that exceed the total extracorporeal clearance of colistin found in our group of patients. The possible presence of residual renal function, differences in the CRRT mode or the higher CRRT dose administered in these two studies might offer a partial explanation for the discrepancies in effluent clearance, although Karvanen et al. also reported an Sc double that found in our patients. The different haemofilters used may have also been responsible: Li et al. and Garton et al. used a 0.9 m² polyacrylonitrile hollow fibre filter (AN 69 HF, Multiflow 100, Hospal, France), which typically carries a pH of 7.4 and displays a negative charge, while the haemofilter used for our study patients had a slightly smaller surface area and a neutrally charged filter membrane.

Karvanen et al. do not provide data on CLapp, but with a daily colistin methane sulphonate dose at least twice that administered to our patients, they achieved lower Cmax values of colistin.
Colistin pharmacokinetics in ICU patients on CVVHDF

Table 1. Pharmacokinetic parameters and clearance of colistin by CVVHDF

<table>
<thead>
<tr>
<th>Patient</th>
<th>CMS dose</th>
<th>Effluent flow rate (mL/h)</th>
<th>Cmax (mg/L)</th>
<th>Cssave (mg/L)</th>
<th>t1/2 (h)</th>
<th>Sc</th>
<th>CLCVVHDF (L/h)</th>
<th>CLEC (L/h)</th>
<th>CLapp (L/h)</th>
<th>CLapp/CLEC (%)</th>
<th>CLCVVHDF/CLEC (%)</th>
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<tr>
<td>1</td>
<td>150 mg/18 h</td>
<td>1900</td>
<td>2.98</td>
<td>1.7</td>
<td>15.7</td>
<td>0.35</td>
<td>0.67</td>
<td>1.93</td>
<td>3.3</td>
<td>59</td>
<td>35</td>
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<td>2</td>
<td>75 mg/8 h</td>
<td>2300</td>
<td>2.29</td>
<td>1.4</td>
<td>8.0</td>
<td>0.35</td>
<td>0.81</td>
<td>1.83</td>
<td>4.3</td>
<td>43</td>
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<tr>
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<td>75 mg/8 h</td>
<td>1950</td>
<td>2.11</td>
<td>1.4</td>
<td>7.7</td>
<td>0.36</td>
<td>0.71</td>
<td>1.99</td>
<td>4.5</td>
<td>45</td>
<td>36</td>
</tr>
</tbody>
</table>

CMS, colistin methane sulphonate; Cmax, maximum colistin serum concentration; Cssave, average concentration at steady state; t1/2, elimination half-life; Sc, sieving coefficient; CLCVVHDF, effluent clearance; CLEC, extracorporeal clearance; CLapp, total (apparent) clearance.

Figure 1. Colistin concentrations achieved in the serum samples (thick lines) and effluent samples (thin lines) of three critically ill patients undergoing CVVHDF following iv administration of colistin methane sulphonate.

Garonzik et al. also reported a very high effluent clearance in their four patients who underwent CVVHD or CVVH (2.06 L/h). Detailed pharmacokinetic data on these patients were not presented, but on the basis of their population pharmacokinetic model, the authors suggested very high daily doses of colistin methane sulphonate to achieve a pharmacodynamic target AUC0–24 to MIC of 60 for colistin, derived from the pharmacodynamic model of Dudhani et al.9,10

The colistin dosage probably resulted in suboptimal concentrations in our patients, with Cssave values ranging from 1.4 to 1.7 mg/L (Table 1), well below the suggested target Cssave of 2.5 mg/L corresponding to a steady-state AUC0–24 of 60 mg·h/L and pharmacodynamic target AUC0–24 to MIC >60 for all but the most susceptible bacteria with an MIC of ≤0.5 mg/L, which is currently often exceeded.11 Admittedly, relatively early sampling in Patient 1, who also had the most protracted t1/2, may have marginally contributed to lower colistin concentrations.

On the other hand, in spite of significant extracorporeal clearance, our patients had considerably reduced total colistin clearance (varying between 3.3 and 4.5 L/h), compared with patients with normal renal function. This suggests that although a higher colistin methane sulphonate dose may have been appropriate in our study, there may still be a need for dose reduction in critically ill patients with ARF treated with CVVHDF. Clearly, further studies are needed to determine the appropriate dosing regimen for colistin methane sulphonate in these patients, taking into account the treatment modality, CRRT dose and residual renal function.

Conclusions

Extracorporeal clearance following iv administration of colistin methane sulphonate resulted in the substantial removal of colistin in three critically ill patients undergoing CVVHDF. The effluent clearance of colistin was found to be similar to that reported in one study, but different from that reported in others. Given the scarcity of information on colistin clearance with different modalities of CRRT and the discrepancies in the existing data, further investigation into colistin pharmacokinetics in this subgroup of patients would be highly desirable. Future studies should evaluate, in addition to effluent clearance, the total extracorporeal clearance of colistin, while any residual renal function should also be taken into account.

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Transparency declarations

None to declare.

References

10 Dudhani RV, Turnidge JD, Nation RL et al. fAUC/MIC is the most predictive pharmacokinetic/pharmacodynamic index of colistin against Acinetobacter baumannii in murine thigh and lung infection models. J Antimicrob Chemother 2010; 5: 1984–90.