Combined Intravenous and Intraventricular Administration of Colistin Methanesulfonate in Critically Ill Patients with Central Nervous System Infection

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Colistin pharmacokinetics were prospectively studied after intravenous administration of colistin methanesulfonate in critically ill patients without central nervous system infection (controls, n = 5) and in patients with external ventricular drain-associated ventriculitis after intravenous administration (EVDViv, n = 3) or combined intravenous/intraventricular administration (EVDVcomb, n = 4). Cerebrospinal fluid (CSF)/serum colistin concentration ratios were higher in EVDViv than in control patients (1.1% versus 7%, P = 0.05) compared to all other patients (P < 0.001). CSF colistin concentrations above the MIC of 0.5 μg/mL were achieved only in EVDVcomb patients.

Previous studies have suggested that the level of antibiotics in the ventricular cerebrospinal fluid (CSF) is important for the outcome of external ventricular drainage (EVD)-related ventriculitis (1–3). The presence of multiresistant bacteria and the poor penetration of many drugs through the blood-brain barrier have imposed the use of intrathecal therapies (4).

Today, colistin, administered as its prodrug colistin methanesulfonate (CMS), is one of the few antibiotics available for treatment of infections by multidrug-resistant Gram-negative organisms. However, intravenous (i.v.) administration is reported to have a relatively poor CSF distribution and clinical outcomes vary (5–7). Data with respect to the efficacy of intraventricular polymyxins, as an add-on therapy, combined with systemic antibiotics are sparse and mainly observational (5, 8).

We aimed to determine the effect of intravenous and combined intravenous/intraventricular CMS administration on colistin concentrations in the CSF and serum in critically ill patients with or without central nervous system (CNS) infection.

This prospective case-controlled randomized study was conducted in a tertiary hospital during a 12-month period between 2011 and 2012. Inclusion criteria were as follows: age ≥ 18 years, diagnosis of EVD-related ventriculitis caused by Gram-negative bacteria, controlled intracranial pressure (<20 mm Hg) for 24 h prior to the study, no renal failure, and no allergy to colistin. Patients with EVD on i.v. CMS treatment for infections by Gram-negative bacteria other than CNS infections were included in the study as controls. The study was approved by the Hospital Ethics and Research Committee and performed in accordance with good clinical practice guidelines.

Control patients received 3,000,000 IU (240 mg) CMS (approximately 90 mg colistin base activity [CIA]) i.v. every 8 h. Patients with EVD-associated ventriculitis caused by Gram-negative bacteria (diagnosed on the basis of clinical grounds plus positive CSF cultures or CSF inflammation, including pleocytosis and a reduced CSF/serum glucose ratio) were randomized to receive the same i.v. dose (EVDViv group), or the i.v. dose combined with 125,000 IU (10 mg) CMS (~3.75 CIA) administered intraventricularly, once daily (EVDVcomb). A 2-mL volume of 6.9% NaCl (volume of catheter lumen) was instilled via the catheter following intraventricular administration, and, at each sampling time, 2 mL of CSF was discarded prior to collection of a CSF sample to avoid CMS carryover. Serum and CSF samples were collected at h 1, 4, and 8 on the first day and at h 1, 4, and 8 on days 3 and 5 after CMS administration. Colistin concentrations were determined using isotopic high-performance liquid chromatography as previously reported (9).

AUC serum and AUC CSF (the area under the concentration-time curve from the time of dosing to the time of the last observation for serum and CSF, respectively) for colistin were estimated from concentration-time data by the linear trapezoidal rule. Data sets were tested for normality (Shapiro–Wilk test), and quantitative variables were compared by using the Mann–Whitney test or t test as appropriate.

Seven patients with ventriculitis and five controls were included; controls received CMS i.v. as part of therapy for pneumonia (n = 4) or bacteremia (n = 1). Table I shows patients’ characteristics. CSF white blood cell counts were elevated in the EVDV comb group; this might indicate severe infection, but no statistically significant difference was found between groups.

CNS administration and CSF collection procedures were well tolerated. No adverse events related to procedures were observed. Isolated pathogens were found to be susceptible to colistin as follows: in members of the control group with pneumonia, Klebsiella pneumoniae (colistin MIC of 2.0 μg/mL) and Acinetobacter baumannii (MIC of 2.0 μg/mL); in those with bacteremia, Acinetobacter baumannii (MIC of 0.5 μg/mL) and in members of the EVDV comb group, Acinetobacter baumannii (MIC of 0.5 μg/mL).
TABLE 1 Clinical data and CSF characteristics of patients in the three study groups at baseline

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Controls (n = 6)</th>
<th>EVDIVv group (n = 9)</th>
<th>EVDIcomb group (n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>46 ± 17</td>
<td>48 ± 14</td>
<td>48 ± 12</td>
</tr>
<tr>
<td>Sex (no. of male/no. of female)</td>
<td>4/1</td>
<td>1/2</td>
<td>3/1</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>82 ± 10</td>
<td>84 ± 16</td>
<td>86 ± 11</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.2 ± 0.5</td>
<td>1.2 ± 0.4</td>
<td>1.3 ± 0.8</td>
</tr>
<tr>
<td>SOFA score</td>
<td>8 ± 4</td>
<td>7 ± 2</td>
<td>7 ± 1</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>32 ± 6</td>
<td>22 ± 6</td>
<td>20 ± 4</td>
</tr>
<tr>
<td>GCS</td>
<td>8 ± 4</td>
<td>7 ± 2</td>
<td>9 ± 4</td>
</tr>
<tr>
<td>CSF characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC (cells/μl)</td>
<td>3 ± 2</td>
<td>344 ± 395</td>
<td>13,650 ± 15,415</td>
</tr>
<tr>
<td>Glu (mg/dl)</td>
<td>79 ± 21</td>
<td>22 ± 19</td>
<td>17 ± 16</td>
</tr>
<tr>
<td>Pr (mg/dl)</td>
<td>64 ± 66</td>
<td>228 ± 123</td>
<td>305 ± 145</td>
</tr>
</tbody>
</table>

*Data are presented as means ± SD or as otherwise indicated. EVDIVv, external ventricular drainage-associated ventriculitis patients treated with i.v. colistin; EVDIcomb, external ventricular drainage-associated ventriculitis patients treated with combined i.v. and intraventricular colistin; SOFA, Sequential Organ Failure Assessment; APACHE, acute physiology and chronic health evaluation; GCS, Glasgow coma scale; WBC, white blood cell; Glu, glucose; Pr, protein.

(n = 1) (two members of the group showed no bacterial growth in culture); and in members of the EVDIcomb group, Acinetobacter baumannii (MIC 0.5) (n = 2) and Klebsiella pneumoniae (MIC 2.0) (n = 5).

On day 1, mean ± SD CSF/serum concentration ratios were higher in the EVDIVv group (b 1, P = 0.05; b 4, P < 0.005; b 8, P < 0.001) than in the control group (Table 2). Similar results were observed on days 3 and 5. Mean AUC CSF/AUC serum ratios were found to be about 60% higher in patients with ventriculitis than in control patients (0.110 versus 0.070). These findings might be indicative of greater colistin penetration in the presence of meningitis.

Complete clinical-microbiological resolution of EVD-related ventriculitis was obtained in one patient in the EVDIVv group and two in the EVDIcomb group (one to the other two only after a change of the initial treatment regimen to intraventricular plus i.v. CMS or aminoglycosides) and in three patients in the EVDIcomb group (one patient presented with refractory EVD-related ventriculitis and died).

On day 1, the means ± standard deviations (SD) of the measured colistin serum concentrations in controls did not differ significantly from those measured in EVDIVv patients (P > 0.05); mean CSF concentrations were higher in EVDIVv patients at all time points, but to a significant (P = 0.009) extent only at b 4 (Table 2).

On day 3, at b 1, mean maximum steady-state colistin concentrations (Cmax, CSF) were similar to those achieved on day 1 in all patients regardless of ventriculitis status (P > 0.05), suggesting a lack of accumulation over time.

On day 1, mean ± SD CSF/serum concentration ratios were higher in the EVDIVv group (b 1, P = 0.05; b 4, P < 0.005; b 8, P < 0.001) than in the control group (Table 2). Similar results were observed on days 3 and 5. Mean AUC CSF/AUC serum ratios were found to be about 60% higher in patients with ventriculitis than in control patients (0.110 versus 0.070). These findings might be indicative of greater colistin penetration in the presence of meningitis.

Colistin Cmax, serum and Cmax, CSF levels in the EVDIcomb group were significantly higher than those achieved in the EVDIVv and control groups (P < 0.0001 and P < 0.0001, respectively). Similarly, median CSF/serum concentration ratios were significantly higher in the EVDIcomb group (P < 0.04) than in the EVDIVv group (0.11) and control group (0.07) (P < 0.0001). Notably, median colistin CSF concentrations were above the MIC of 0.5 μg/ml in the EVDIcomb patient group (1.4 μg/ml range, 0.6 to 1.6 μg/ml), but not the EVDIVv patient group (0.14 μg/ml range, 0.07 to 0.3 μg/ml), at all time points. Therefore, combined i.v.-intraventricular treatment can augment colistin levels in CSF, which is in agreement with recent data reported by Imberti et al. (10).

TABLE 2 Colistin concentration-time data for the different study groups

<table>
<thead>
<tr>
<th>Study group</th>
<th>Day</th>
<th>Time [h]</th>
<th>No. of samples</th>
<th>Mean ± SD (μg/ml) (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Serum</td>
</tr>
<tr>
<td>Control</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>2.038 ± 0.348</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>5</td>
<td></td>
<td>1,491 ± 74</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>5</td>
<td></td>
<td>1,041 ± 135</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>2,039 ± 5.4</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>1</td>
<td></td>
<td>1,033</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>1</td>
<td></td>
<td>2,013</td>
</tr>
<tr>
<td>EVDIVv</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2,189 (1,922–2,455)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>2</td>
<td></td>
<td>1,461 (1,461–1,461)</td>
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<td></td>
<td>8</td>
<td>2</td>
<td></td>
<td>1,099 (1,050–1,268)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>2</td>
<td></td>
<td>2,255 (2,097–2,313)</td>
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<td></td>
<td>8</td>
<td>2</td>
<td></td>
<td>1,001 (1,000–1,032)</td>
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<tr>
<td></td>
<td>9</td>
<td>1</td>
<td></td>
<td>2,489</td>
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<td></td>
<td>8</td>
<td>1</td>
<td></td>
<td>1,258</td>
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<tr>
<td>EVDIcomb</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>3,451 ± 221</td>
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<tr>
<td></td>
<td>4</td>
<td>1</td>
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<td>1,858</td>
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<td>8</td>
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<td>1,523</td>
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<td>3,144</td>
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<td>5</td>
<td>3</td>
<td></td>
<td>3,051 ± 205</td>
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<tr>
<td></td>
<td>8</td>
<td>3</td>
<td></td>
<td>1,914 (1,415–1,612)</td>
</tr>
</tbody>
</table>

*Data are presented as means ± SD or as otherwise indicated. EVDIVv, external ventricular drainage-associated ventriculitis patients treated with i.v. colistin; EVDIcomb, external ventricular drainage-associated ventriculitis patients treated with combined i.v. and intraventricular colistin.
These data suggest the superiority of combined i.v.-intra-
ventricular treatment to i.v. treatment alone and that com-
bined treatment is more likely to effectively eradicate Gram-
negative bacilli from the CNS. Notably, the clinical response
rate with combined treatment was 75% in this study; we ac-
knowledge that our study was not sufficiently powered and
thus, that definitive conclusions at the clinical level could be
drawn from adequately powered studies in the future. Fur-
thermore, the optimal dose and duration of intraventricular CMS
therapy (commonly 40,000 to 500,000 IU/day [approximately
1.2 to 15.0 CBA]) remain undetermined (11). Nevertheless,
our data suggest that combined intravenous-intrathecal treat-
ment may achieve higher levels in CSF, which may be crucial in
controlling multidrug-resistant infections.

A plausible explanation(s) for the higher colistin CSF con-
centrations in the IV/IVD group—apart from the administration
of the intraventricular CMS dose—could be higher protein bind-
ing (given increased protein concentrations) or increased men-
ingeal permeability. We hypothesize that the higher plasma colis-
tin concentrations in this group are due to almost the whole
intraventricular CMS dose being transferred to colistin in the
CSF (creating a CSF-to-plasma concentration gradient) and then
passing through the blood-brain barrier, in contrast to the in-
travenous dose, where a large amount (79% to 93%) of the CMS dose
is renally or otherwise eliminated prior to its conversion to colis-
tin. Therefore, the amount of colistin remaining in the body is the
sum of almost the whole dose administered intraventricularly and
the proportion (7% to 30% converted) (12-14) of the dose ad-
ministered intravenously.

Another point that should be underscored is that CMS penetra-
tion and exertion of action in the CNS, as well as the elimination
might be poor. The median colistin CSF/serum concentration ratio in
our control patients was 0.07. This is comparable to that reported
previously in critically ill patients with minimal CSF inflamma-
tion at the time of sampling (0.05 to 0.07) (4).

On the other hand, we found no evidence of drug accumula-
tion over time such as one might have expected; and the decline in
concentration between 0.4 and 8 hours suggests a shorter half-life
(1/2) of elimination than in previous pharmacokinetic studies in serum
(15). The small population size in our study or the considerable
fluctuations of steady-state concentrations of colistin throughout
the dosage interval might explain these differences.

In conclusion, our findings suggest that the intravenous ad-
ministration of CMS in critically ill patients with EVD-associated
ventriculitis caused by Gram-negative bacteria provided a maxi-
num concentration of colistin in CSF of 11% of that present in
serum. In contrast, combined intraventricular-i.v. administration
of CMS resulted in higher CSF levels of the drug which were above
the MIC of one of the targeted pathogens, Acinetobacter bauman-
nii, throughout the dosing interval, suggesting that this treatment
modality may be considered in cases of EVD-related ventriculitis
caused by Gram-negative bacteria, where high drug levels in the
ventricles are important.

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and at the Laboratory of Biopharmaceutics and Pharmacokinetics, Fac-
sity of Pharmacy, University of Athens.

We declare that we have no conflicts of interest.

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