COMBINED INTRAVENOUS AND INTRAVENTRICULAR ADMINISTRATION OF COLISTIN METHANE SULPHONATE IN CRITICALLY ILL PATIENTS WITH CNS INFECTION

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Running title: IV and intraventricular use of CMS in ventriculitis

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The authors declare no conflict of interest

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ABSTRACT

Colistin pharmacokinetics were prospectively studied after intravenous administration of colistin methanesulphonate 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 compared to controls (11% vs. 7%, p≤0.05), and in EVDVcomb compared to all other patients (p<0.0001). CSF colistin concentrations >MIC 0.5μg/ml achieved only in EVDVcomb.

Keywords: ventriculitis, gram negative pathogens, colistin, intraventricular therapy, pharmacokinetics, ICU
Abbreviations:

AUC: Areas under the concentration curves

CMS: Colistin methanesulphonate

CNS: Central Nervous System

CSF: Cerebrospinal Fluid

EVD: External ventricular drain

EVDViv: External ventricular drainage associated ventriculitis treated with iv colistin methanesulphonate

EVDVcomb: External ventricular drainage associated ventriculitis treated with combination of iv and intraventricular colistin methanesulphonate

HPLC: High-Performance Liquid Chromatography

ICP: Intracranial Pressure

iv: intravenous

MDR: Multi Drug Resistant

SAH: Subarachnoid Haemorrhage
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 (7,14,15). The presence of multiresistant bacteria and the poor penetration of many drugs through the blood–brain barrier have imposed the use of intrathecal therapies (13).

Today, colistin administered as its prodrug colistin methanesulphonate (CMS) is one of the few antibiotics available for infections from multidrug-resistant gram-negative organisms. However, intravenous (iv) administration is reported to have a relatively poor CSF distribution and clinical outcomes vary (5,8,10). Data with respect to the efficacy of intraventricular polymyxins, as add-on therapy, combined with systemic antibiotics, are sparse and mainly observational (2,5).

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 2011-2012. Inclusion criteria were: age >18 years-old, EVD gram-negative bacteria ventriculitis diagnosis, controlled intracranial pressure (<20mmHg) for 24 hours prior to the study, no renal failure, no allergy to colistin. Patients with EVD on CMS iv for gram-negative other than CNS bacterial 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 (240mg) CMS (approximately 90mg colistin base activity (CBA), iv every 8h. Patients with EVD Gram negative bacterial ventriculitis (based on clinical grounds plus positive CSF cultures or CSF inflammation, including pleocytosis and a reduced CSF/serum glucose ratio), were randomized to receive the same iv dose (EVDViv group) or, the iv dose combined with 125,000 IU (10mg) CMS (~3.75 CBA) intraventricularly, once daily (EVDVcomb). Two ml of NS 0.9% (volume of catheter lumen) were instilled via the catheter following intraventricular administration and at each sample time 2 ml CSF were discarded prior to collection of CSF sample to avoid CMS carryover. Serum and CSF samples were collected at 1st, 4th, 8th hours on the first day and at 1st, 8th hours on the third and fifth day after CMS administration. Colistin concentrations were determined using isocratic high-performance liquid chromatography as reported(11). AUCserum and AUCCSF (the area under the 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 linear trapezoidal rule. Data sets were tested for normality (Shapiro-Wilk test), 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 iv as part of therapy for pneumonia (n=4), bacteremia (n=1). Table 1 shows participants’ characteristics. CSF white blood cells were elevated in EVDVcomb group; this might indicate severe infection but no statistically significant difference was found between groups. CMS 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: control group–pneumonia [(Klebsiella pneumoniae, MIC
2.0)(n=1), (Acinetobacter baumannii, MIC 2.0,2.0,0.5)(n=3)], bacteraemia

[(Acinetobacter baumannii, MIC 0.5)(n=1)]; EVDViv group [Acinetobacter baumannii (MIC 0.5)(n=1), no bacterial growth in culture (n=2)]; EVDVcomb

[(Acinetobacter baumannii, MIC 0.5)(n=2), (Klebsiella pneumoniae, MIC 2.0)(n=2)]. Complete clinical – microbiological resolution of EVD-ventriculitis was

obtained in one patient in EVDViv group (and in the other two only after the change

of initial treatment regimen to intraventricular plus iv CMS or aminoglycosides) and in three patients in EVDVcomb group (one patient presented refractory EVD-

ventriculitis and died).

On day 1, the mean±SD measured colistin serum concentrations in controls did

not differ significantly from EVDViv patients (p>0.05); mean CSF concentrations were higher in EVDViv patients at all time points, but only at the 4th hour to a

significant extent (p=0.009) (Table 2).

On day 3, at the 1st hour, mean maximum steady state colistin concentrations

(CmaxCSF) were similar to those achieved on day 1 in all patients regardless of

ventriculitis (p>0.05) suggesting lack of accumulation over time.

On Day 1, mean±SD, CSF/SERUM concentration ratios were higher in the

EVDViv group [1st hour (p=0.05), 4th hour (p<0.005) and 8th hour (p<0.001)] compared with controls (Table 2). Similar results were also observed on days 3 and 5. Mean

AUCCSF/ AUC SERUM ratios were found to be about 60% higher in patients with

ventriculitis compared to controls (0.110 vs. 0.070). These findings might be

indicative of greater colistin penetration in the presence of meningeal inflammation.

Colistin Cmaxserum and CmaxCSF in EVDVcomb group were significantly

higher compared to those achieved in EVDViv and control groups (p <0.0001 and

p<0.0001, respectively). Similarly, median CSF/SERUM concentration ratios were
significantly higher in the EVDVcomb group (≥0.40) compared to those in the EVDViv group (0.11) and controls (0.07) (p<0.0001). Notably, median(range) colistin CSF concentrations were above MIC 0.5μg/ml in the EVDVcomb patients [1.4(0.6–1.6) μg/ml], but not the EVDViv patients [0.14(0.07–0.3) μg/ml], at all time points. Therefore, combined iv-intrathecal treatment can augment colistin levels in CSF which is in agreement with recent data reported by Imberti et al(3).

These data suggest superiority of combined iv-intraventricular treatment over iv treatment alone and that combined 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 acknowledge that our study was not sufficiently powered and thus definitive conclusions at the clinical level could be drawn from adequately powered studies in the future. Furthermore, the optimal dose and duration of intraventricular CMS therapy (commonly 40.000 to 500000 IU/day, approximately 1.2-15.0CBA), remains undetermined(4). Nevertheless, our data suggests that combined intravenous-intrathecal treatment may achieve higher levels in CSF which may be crucial in controlling multidrug resistant infections.

Plausible explanations for the higher colistin CSF concentrations in the EVDVcomb group -apart from the administration of the intraventricular CMS dose- could be due to higher protein binding (given increased protein concentrations) or to increased membrane permeability. We hypothesize that the higher plasma colistin concentrations in this group are due to almost the whole intraventricular CMS dose being transformed to colistin in the CSF (creating a CSF to plasma concentration gradient) and then passing through the blood-brain barrier, in contrast to the intravenous dose, where a large amount of the CMS dose is renally or otherwise eliminated prior to its conversion to colistin (70-93%). Therefore the amount of
colistin remaining in the body is the sum of almost the whole dose administered intraventricularly and the percentage (7-30% converted)(1,6,9) of the dose administered intravenously.

Another point that should be underlined is that CMS penetration in the meninges in the absence of inflammation might be poor. 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 inflammation at the time of sampling (0.05-0.057)(13).

On the other hand, we found no evidence of drug accumulation over time as one might have expected and the decline in concentrations between the 4th-8th hour suggests a smaller t½ of elimination compared to previous pharmacokinetic studies in serum(12). The small population size in our study or considerable fluctuations of steady state concentrations of colistin throughout the dosage interval might explain these differences.

In conclusion, our findings suggest that the intravenous administration of CMS in critically ill patients with EVD-associated Gram negative bacterial ventriculitis provided a maximum concentration of colistin in CSF of 11% of that present in serum. In contrast, combined intraventricular-iv administration of CMS resulted in higher CSF levels of the drug which were above the MIC of one of the targeted pathogens, \textit{Acinetobacter baumannii}, throughout the dosing interval, suggesting that this treatment modality may be considered in gram negative bacterial EVD-ventriculitis where high drug levels in the ventricles are important.
References


Table 1. Clinical data and CSF characteristics of patients in the three study groups at baseline

<table>
<thead>
<tr>
<th></th>
<th>Controls (N=5)</th>
<th>EVDViv group (N=3)</th>
<th>EVDVcomb group (N=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (y)</strong></td>
<td>46±17</td>
<td>48±14</td>
<td>48±12</td>
</tr>
<tr>
<td><strong>Sex (Male/Female)</strong></td>
<td>4M/1F</td>
<td>1M/2F</td>
<td>3M/1F</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>82±10</td>
<td>84±16</td>
<td>86±11</td>
</tr>
<tr>
<td><strong>Creatinine (mg/dl)</strong></td>
<td>1.2±0.6</td>
<td>1.2±0.4</td>
<td>1.3±0.8</td>
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<tr>
<td><strong>SOFA score</strong></td>
<td>8±4</td>
<td>7±2</td>
<td>7±1</td>
</tr>
<tr>
<td><strong>APACHE II score</strong></td>
<td>22±6</td>
<td>22±6</td>
<td>20±4</td>
</tr>
<tr>
<td><strong>GCS</strong></td>
<td>8±4</td>
<td>7±1</td>
<td>9±4</td>
</tr>
<tr>
<td><strong>CSF characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>WBC (cells/μl)</strong></td>
<td>3±2</td>
<td>344±395</td>
<td>13650±15415</td>
</tr>
<tr>
<td><strong>Glu (mg/dl)</strong></td>
<td>79±25</td>
<td>22±19</td>
<td>17±16</td>
</tr>
<tr>
<td><strong>Pr (mg/dl)</strong></td>
<td>64±60</td>
<td>228±123</td>
<td>305±145</td>
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</tbody>
</table>

Data are presented as mean ± SD or otherwise indicated; EVDViv, external ventricular drainage associated ventriculitis patients treated with iv colistin; EVDVcomb, external ventricular drainage associated ventriculitis patients treated with combined iv 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.
Table 2. Colistin concentration – time data for the different study groups

<table>
<thead>
<tr>
<th>Day</th>
<th>Time (hours)</th>
<th>N of samples</th>
<th>Serum (ng/ml) Mean ± SD (range)</th>
<th>CSF (ng/ml)</th>
<th>CSF/SERUMratio</th>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Controls</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>2308 ±348</td>
<td>152 ±18</td>
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<tr>
<td></td>
<td>4</td>
<td>5</td>
<td>1491±74</td>
<td>105±11</td>
<td>0.070 ± 0.006</td>
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<tr>
<td></td>
<td>8</td>
<td>5</td>
<td>1041±135</td>
<td>76±11</td>
<td>0.074± 0.002</td>
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<tr>
<td></td>
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<td>3</td>
<td>2039±4</td>
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<tr>
<td></td>
<td>8</td>
<td>1</td>
<td>1033</td>
<td>72</td>
<td>0.070</td>
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<tr>
<td></td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>2013</td>
<td>137</td>
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<tr>
<td>EVDViv</td>
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<td>2</td>
<td>2189 (1922-2455)</td>
<td>237 (198-275)</td>
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<tr>
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<td>2</td>
<td>1451 (1405-1498)</td>
<td>156 (152-159)</td>
<td>0.107</td>
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<td>1089 (930-1248)</td>
<td>120 (103-137)</td>
<td>0.110</td>
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<tr>
<td></td>
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<td>1</td>
<td>2</td>
<td>2205 (2097-2313)</td>
<td>254 (213-295)</td>
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<tr>
<td></td>
<td>8</td>
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<td>1001 (970-1032)</td>
<td>119 (117-120)</td>
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<td>1</td>
<td>1</td>
<td>2449</td>
<td>259</td>
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<td>8</td>
<td>1</td>
<td>1258</td>
<td>140</td>
<td>0.111</td>
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<tr>
<td>EVDVcomb</td>
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<td>3451±221</td>
<td>1449±124</td>
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<td>1838</td>
<td>838</td>
<td>0.456</td>
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<td>621</td>
<td>0.408</td>
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<td>1</td>
<td>3144</td>
<td>1357</td>
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<td>5</td>
<td>1</td>
<td>3</td>
<td>3531±202</td>
<td>1430±40</td>
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<tr>
<td></td>
<td>8</td>
<td>2</td>
<td>1514 (1415-1612)</td>
<td>611 (548-675)</td>
<td>0.403</td>
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</tbody>
</table>

Data are presented as mean ± SD or otherwise indicated; EVDViv, external ventricular drainage associated ventriculitis patients treated with iv colistin; EVDVcomb, external ventricular drainage associated ventriculitis patients treated with combined iv and intraventricular colistin.