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 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 than in control patients (11% versus 7%, $P \leq 0.05$) and in EVDVcomb compared to all other patients ($P < 0.0001$). 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 [CBA]) 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 CBA) administered intraventricularly, once daily (EVDVcomb). A 2-ml volume of 0.9% NaCl

(volume of catheter lumen) was instilled via the catheter following intraventricular administration, and, at each sample 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 and 8 on days 3 and 5 after CMS administration. Colistin concentrations were determined using isocratic 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 1 shows participants' characteristics. CSF white blood cell counts were elevated in the 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 as follows: in members of the control group with pneumonia, *Klebsiella pneumoniae* (colistin MIC of 2.0) ($n = 1$) and *Acinetobacter baumannii* (MIC of 2.0, 2.0, and 0.5) ($n = 3$), and in those with bacteremia, *Acinetobacter baumannii* (MIC 0.5) ($n = 1$); in members of the EVDViv group, *Acinetobacter baumannii* (MIC 0.5)

TABLE 1 Clinical data and CSF characteristics of patients in the three study groups at baseline[a]

Parameter	Value		
	Controls ($n = 5$)	EVDViv group ($n = 3$)	EVDVcomb group ($n = 4$)
Age (yr)	46 ± 17	48 ± 14	48 ± 12
Sex (no. of males/no. of females)	4/1	1/2	3/1
Weight (kg)	82 ± 10	84 ± 16	86 ± 11
Creatinine (mg/dl)	1.2 ± 0,5	1.2 ± 0.4	1.3 ± 0.8
SOFA score	8 ± 4	7 ± 2	7 ± 1
APACHE II score	22 ± 6	22 ± 6	20 ± 4
GCS	8 ± 4	7 ± 1	9 ± 4
CSF characteristics			
WBC (cells/μl)	3 ± 2	344 ± 395	13,650 ± 15,415
Glu (mg/dl)	79 ± 25	22 ± 19	17 ± 16
Pr (mg/dl)	64 ± 60	228 ± 123	305 ± 145

[a] Data are presented as means ± SD or as otherwise indicated. EVDViv, external ventricular drainage-associated ventriculitis patients treated with i.v. colistin; EVDVcomb, 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 EVDVcomb group, *Acinetobacter baumannii* (MIC 0.5) ($n = 2$) and *Klebsiella pneumoniae* (MIC 2.0) ($n = 2$).

Complete clinical-microbiological resolution of EVD-related ventriculitis was obtained in one patient in the EVDViv group (and in 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 EVDVcomb 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 EVDViv patients ($P > 0.05$); mean CSF concentrations were higher in EVDViv patients at all time points, but to a significant ($P = 0.009$) extent only at h 4 (Table 2).

On day 3, at h 1, mean maximum steady-state colistin concentrations (C_{max} 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 EVDViv group (h 1, $P = 0.05$; h 4, $P < 0.005$; h 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 meningeal inflammation.

Colistin C_{max} serum and C_{max} CSF levels in the EVDVcomb group were significantly higher than those achieved in the 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) than in the EVDViv 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 EVDVcomb patient group (1.4 μg/ml [range, 0.6 to 1.6 μg/ml]), but not the EVDViv patient group (0.14 μg/ml [range, 0.07 to 0.3 μg/ml]), at all time points. Therefore, combined i.v.-intrathecal 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[a]

Study group	Day	Time (h)	No. of samples	Mean ± SD (ng/ml) (range)		CSF/serum ratio
				Serum	CSF	
Control	1	1	5	2,308 ± 348	152 ± 18	0.066 ± 0.002
		4	5	1,491 ± 74	105 ± 11	0.070 ± 0.006
		8	5	1,041 ± 135	76 ± 11	0.074 ± 0.002
	3	1	3	2,039 ± 4	141 ± 17	0.069 ± 0.001
		8	1	1,033	72	0.070
	5	1	1	2,013	137	0.068
EVDViv	1	1	2	2,189 (1,922–2,455)	237 (198–275)	0.108
		4	2	1,451 (1,405–1,498)	156 (152–159)	0.107
		8	2	1,089 (930–1,248)	120 (103–137)	0.110
	3	1	2	2,205 (2,097–2,313)	254 (213–295)	0.114
		8	2	1,001 (970–1,032)	119 (117–120)	0.118
	5	1	1	2,449	259	0.106
		8	1	1,258	140	0.111
EVDVcomb	1	1	3	3,451 ± 221	1,449 ± 124	0.420 ± 0.012
		4	1	1,838	838	0.456
		8	1	1,523	621	0.408
	3	1	1	3,144	1,357	0.432
	5	1	3	3,531 ± 202	1,430 ± 40	0.406 ± 0.012
		8	2	1,514 (1,415–1,612)	611 (548–675)	0.403

[a] Data are presented as means ± SD or as otherwise indicated. EVDViv, external ventricular drainage-associated ventriculitis patients treated with i.v. colistin; EVDVcomb, external ventricular drainage-associated ventriculitis patients treated with combined i.v. and intraventricular colistin.

These data suggest the superiority of combined i.v.-intraventricular treatment to i.v. treatment alone and that combined treatment is more likely to effectively eradicate Gramnegative 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, that 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 500,000 IU/day [approximately 1.2 to 15.0 CBA]) remain undetermined (11). Nevertheless, our data suggest that combined intravenous-intrathecal treatment may achieve higher levels in CSF, which may be crucial in controlling multidrug-resistant infections.

A plausible explanation(s) for the higher colistin CSF concentrations in the EVDVcomb group—apart from the administration of the intraventricular CMS dose—could be higher protein binding (given increased protein concentrations) or 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 (70% to 93%) of the CMS dose is renally or otherwise eliminated prior to its conversion to colistin. 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 administered intravenously.

Another point that should be underlined is that CMS penetration in the meninges in the absence of inflammation 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 inflammation at the time of sampling (0.05 to 0.057) (4).

On the other hand, we found no evidence of drug accumulation over time such as one might have expected, and the decline in concentrations between h 4 and 8 suggests a smaller half-life ($t_{1/2}$) 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 administration of CMS in critically ill patients with EVD-associated ventriculitis caused by Gram-negative bacteria provided a maximum 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 baumannii*, 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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