Pharmacokinetics of Colistin in Cerebrospinal Fluid after Intraventricular Administration of Colistin Methanesulfonate

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Intraventricular colistin, administered as colistin methanesulfonate (CMS), is the last resource for the treatment of central nervous system infections caused by panresistant Gram-negative bacteria. The doses and daily regimens vary considerably and are empirically chosen; the cerebrospinal fluid (CSF) pharmacokinetics of colistin after intraventricular administration of CMS has never been characterized. Nine patients (aged 18 to 73 years) were treated with intraventricular CMS (daily doses of 2.61 to 10.44 mg). Colistin concentrations were measured using a selective high-performance liquid chromatography (HPLC) assay. The population pharmacokinetics analysis was performed with the P-Pharm program. The pharmacokinetics of colistin could be best described by the one-compartment model. The estimated values (means ± standard deviations) of apparent CSF total clearance (CL/Fm, where Fm is the unknown fraction of CMS converted to colistin) and terminal half-life (t1/2) were 0.033 ± 0.014 liter/h and 7.8 ± 3.2 h, respectively, and the average time to the peak concentration was 3.7 ± 0.9 h. A positive correlation between CL/Fm and the amount of CSF drained (range 40 to 300 ml) was observed. When CMS was administered at doses of ≥5.22 mg/day, measured CSF concentrations of colistin were continuously above the MIC of 2 μg/ml, and measured values of trough concentration (Ctrough) ranged between 2.0 and 9.7 μg/ml. Microbiological cure was observed in 8/9 patients. Intraventricular administration of CMS at doses of ≥5.22 mg per day was appropriate in our patients, but since external CSF efflux is variable and can influence the clearance of colistin and its concentrations in CSF, the daily dose of 10 mg suggested by the Infectious Diseases Society of America may be more prudent.

Central nervous system infections (meningitis, ventriculitis, and abscesses) caused by Gram-negative bacteria are a therapeutic challenge. These infections generally occur in patients during their hospital stay and are secondary to neurosurgical or otorhinologic procedures, head trauma, and rarely, to metastatic infections from bacteremia (28). Their treatment has been further complicated by the emergence of Gram-negative bacteria, generally Acinetobacter baumannii, Pseudomonas aeruginosa, and Klebsiella pneumoniae, which are resistant to expanded-spectrum and “fourth-generation” cephalosporins, aminoglycosides, and carbapenems (19). Under these conditions, the treatment relies on polymyxins, such as colistin. Colistin is a bactericidal, concentration-dependent antimicrobial agent with a modest postantibiotic effect (20). Although the pharmacodynamic parameters best predicting the efficacy of colistin have not yet been established in humans, in vitro and in vivo animal studies have suggested that the area under the curve (AUC)/MIC ratio of total and unbound colistin is the index that best predicts the antibacterial activity against P. aeruginosa (3, 7, 8). Colistin is usually administered as colistin methanesulfonate (CMS). CMS, which is inactive, is converted to colistin (the active form with antimicrobial activity) both in vitro and in vivo by hydrolysis of methanesulfonate radicals (2, 4). Data available from the literature indicate that in humans, the penetration of CMS and colistin into cerebrospinal fluid (CSF) is poor, both in patients with uninflamed and those with inflamed meninges (11). Reported CSF-to-serum concentration ratios are 0.051 to 0.057 (21) and 0.16 (estimated from the data shown in Fig. 1) (11). CMS is, therefore, generally administered via the intraventricular (IVT) or intrathecal route alone or in association with the systemic route (for a comprehensive review, see reference 9). The dosages of IVT/intrathecal colistin are empirically chosen and range between 1.6 and 40 mg, as a single dose or in divided doses (9, 13). Guidelines published by the Infectious Diseases Society of America (IDSA) in 2004 suggest that the IVT dosage of colistin (presumably CMS) should be 10 mg (27), but the optimal IVT/intrathecal dosing regimen for CMS remains unknown.

To our knowledge, the pharmacokinetics of colistin after IVT administration of CMS has never been characterized. Moreover, it is not known whether colistin accumulates in CSF following repeated IVT doses (as used clinically).

Since CNS infections caused by panresistant Gram-negative bacteria occur relatively infrequently, a detailed description of the pharmacokinetics of colistin after IVT administration of CMS will require many centers and a considerable period of time. We therefore deemed it appropriate to present these preliminary results.
MATERIALS AND METHODS

Study population. The pharmacokinetics of colistin was evaluated in 9 adult patients (aged 18 to 73 years; 6 males, 3 females) who, during their hospital stay, developed central nervous system infection by panresistant Acinetobacter baumannii (6 patients), Carbapenem-resistant Klebsiella pneumoniae (2 patients), or Carbapenem-resistant Pseudomonas aeruginosa (1 patient). A bacteriological diagnosis of central nervous system infection was obtained after sampling patients in a conscious condition or on the day of sampling ranged from 3 to 11.

TABLE 1 Demographic and clinical characteristics and outcomes of the patients

<table>
<thead>
<tr>
<th>CMS dose (mg)/schedule</th>
<th>Admission diagnosis</th>
<th>Day of sampling</th>
<th>MIC for colistin (µg/ml)</th>
<th>AUC_{0–16}\text{mcg.h/mL}</th>
<th>Duration of IVT therapy (days)</th>
<th>Microbiology</th>
<th>ICU outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.61 mg/12 h (2 patients) and 5.22 mg/12 h (3 patients)</td>
<td>SAH</td>
<td>10</td>
<td>0.5 CMS</td>
<td>1.20</td>
<td>1</td>
<td>Cured</td>
<td>Survival</td>
</tr>
<tr>
<td>5.22 mg/24 h (2 patients)</td>
<td>Aneurysmal SAH and ICH EVD</td>
<td>50</td>
<td>2 CMS, linezolid</td>
<td>15</td>
<td>36</td>
<td>Cure</td>
<td>Survival</td>
</tr>
<tr>
<td>2.61 mg/24 h (1 patient)</td>
<td>SAH</td>
<td>65</td>
<td>2 CMS, meropenem, linezolid</td>
<td>36</td>
<td>65</td>
<td>Failure</td>
<td>Death unrelated</td>
</tr>
<tr>
<td>2.61 mg/24 h (1 patient)</td>
<td>SAH</td>
<td>65</td>
<td>2 Ceftazidime</td>
<td>24</td>
<td>65</td>
<td>Cure</td>
<td>Survival</td>
</tr>
<tr>
<td>2.61 mg/24 h (1 patient)</td>
<td>SAH</td>
<td>65</td>
<td>2 Amikacin, ceftazidime</td>
<td>31</td>
<td>65</td>
<td>Cure</td>
<td>Survival</td>
</tr>
<tr>
<td>2.61 mg/24 h (1 patient)</td>
<td>SAH</td>
<td>65</td>
<td>2 Meropenem, ampicillin-sulbactam</td>
<td>31</td>
<td>65</td>
<td>Failure</td>
<td>Death unrelated</td>
</tr>
<tr>
<td>2.61 mg/24 h (1 patient)</td>
<td>SAH</td>
<td>65</td>
<td>2 Ceftazidime</td>
<td>18</td>
<td>65</td>
<td>Cure</td>
<td>Survival</td>
</tr>
<tr>
<td>2.61 mg/12 h (1 patient)</td>
<td>SAH</td>
<td>65</td>
<td>2 CMS, rifampin</td>
<td>27</td>
<td>65</td>
<td>Cure</td>
<td>Survival</td>
</tr>
<tr>
<td>2.61 mg/24 h (1 patient)</td>
<td>SAH</td>
<td>65</td>
<td>2 Meropenem, ampicillin-sulbactam</td>
<td>31</td>
<td>65</td>
<td>Failure</td>
<td>Death unrelated</td>
</tr>
<tr>
<td>2.61 mg/12 h (1 patient)</td>
<td>SAH</td>
<td>65</td>
<td>2 CMS, meropenem</td>
<td>36</td>
<td>65</td>
<td>Cure</td>
<td>Survival</td>
</tr>
<tr>
<td>2.61 mg/12 h (1 patient)</td>
<td>SAH</td>
<td>65</td>
<td>2 Ceftazidime</td>
<td>24</td>
<td>65</td>
<td>Cure</td>
<td>Survival</td>
</tr>
</tbody>
</table>

Note: CMS, colistin methanesulfonate; SAH, subarachnoid hemorrhage; CMS, colistin methanesulfonate; EVD, external ventricular drainage; ICH, intracerebral hemorrhage; ICU, intensive care unit; SAPS II, simplified acute physiology score II; STBI, severe traumatic brain injury.
Potential nephrotoxicity was assessed by daily measurements of creatinine clearance.

**Chemicals and reagents.** Colistin sulfate salt, trifluoroacetic acid (TFA) and 9-fluorenylmethyl chloroformate (FMOC-CL) were purchased from Sigma-Aldrich (St. Louis, MO), and Sep-Pak SPE cartridges were obtained from Waters (Waters, Milford, MA). Polypropylene tubes were purchased from Eppendorf (Milano, Italy). High-performance liquid chromatography (HPLC)-grade methanol, acetoni trate, tetrahydrofuran, and acetonitrile were purchased from Carlo Erba Reagents (Milan, Italy). Water was purified with a Milli Q system (Millipore, Bedford, MA). CMS (Colimicina) was purchased from UCB Pharma, Pianezza, Italy.

**Conversion of CMS to colistin in vitro in human CSF.** Concentration-dependent hydrolysis of CMS was studied by storing CMS solutions at different concentrations. Blank human CSF (250 μl) was spiked with CMS at concentrations of 10, 20, 50, 100, and 200 μg/ml and kept at 37°C. Assuming that the total volume of CSF in adult humans is 150 ml (5, 23), the daily dose of CMS administered IVT to our patients was within this range. At 0.5, 1, 2, 4, 8, and 16 h, samples (250 μl) were removed and analyzed immediately. The levels of colistin formed by hydrolysis of CMS were assayed by HPLC as described below.

The percentage of colistin formed by hydrolysis of CMS was calculated on a molar basis. In the present study, the molecular weights of colistin A and colistin B were set at 1,170 and 1,156, respectively. The molecular weight of CMS was set at 1,743.

**Pharmacokinetic procedures.** The colistin concentrations in CSF were evaluated after at least 2 days of treatment with CMS. CSF samples were obtained immediately before and at 10 min and 1, 2, 4, 8, and 12 h after the bolus in patients receiving CMS every 12 h and immediately before and at 10 min and 1, 2, 4, 8, 12, 16, and 24 h after the bolus in patients receiving CMS every 24 h. The concentrations of colistin in CSF were also evaluated just before CMS administration in the 3 days following the day of the pharmacokinetic studies to evaluate the possibility of colistin accumulation. CSF samples were collected and stored in polypropylene tubes at −80°C until analysis. The maximum time that CSF was stored at −80°C was 3 months.

**Colistin assay.** Colistin in CSF was measured using the method described by Li et al. (18) with minor modifications (10). This is a sensitive method which discriminates colistin from CMS. The concentration of colistin was determined by HPLC with fluorescence detector. An aliquot (250 μl) of CSF was vortex-mixed in a polypropylene tube with internal standard (10 μl of 10 mg/liter netilmicin sulfate), 50 μl TFA (50/50, vol/vol) solution, and centrifuged (4°C at 1,000 × g for 10 min). The supernatant was loaded into a Sep-Pak cartridge preconditioned with methanol and equilibrated with carbonate buffer. Colistin was derivatized with FMOC-CL (60 μl) in SPE C18 cartridges, eluted with acetonitrile, and evaporated under a nitrogen stream. Samples were reconstituted (boric acid and mobile phase), and 25-μl amounts injected into the HPLC system. Separation was performed on a Zorbax SB-C18, 4.6×25 cm column. The mobile phase consisted of acetonitrile, tetrahydrofuran, and water delivered isocratically at 1 ml/min.

The calibration curve was linear between 0.4 and 10 μg/ml. The intra-assay and interassay variabilities were <10% and 12%, respectively. The lower limit of quantification (LOQ) was 0.1 μg/ml. The recovery, calculated by comparing the responses (the slopes of the lines describing the change in derivatized colistin to internal standard as increasing amounts of colistin were added to the samples) from CSF with those from water, was 104.8% ± 1.2% (mean ± standard deviation [SD]) (n = 3). The validation of the method in a CSF matrix was performed according to the Guidance for Industry document “Bioanalytical Method Validation” issued by the FDA in May 2001 (http://www.fda.gov/downloads/Drugs /GuidanceComplianceRegulatoryInformation/Guidances/UCM070107. pdf).

**CSF pharmacokinetic analysis.** The colistin CSF data were used to construct the model and to estimate the pharmacokinetic parameters of colistin intraventricularly administered as CMS. A one-compartment model with input and output from a central IVT compartment was used to analyze the data (Fig. 2). The input was characterized by the extent and by the formation rate constant of colistin from CMS. The output consisted of one elimination rate constant, describing both the diffusion of colistin from the CSF to the systemic circulation and its elimination through the external ventricular drainage flow. The pharmacokinetic parameters were: kf (first-order rate constant for CMS conversion to colistin), t1/2f (formation half-life of colistin from CMS), CL/Fm (apparent total CSF clearance of colistin after IVT administration of CMS corrected by Fm, the unknown fraction of CMS converted to colistin), V/Fm (apparent CSF volume of distribution of colistin corrected by Fm), k10 (first-order removal rate constant of colistin from CSF), and t1/2h (terminal half-life of formed colistin).

The maximum steady-state concentration (Cmax) achieved in CSF during a dosage interval (τ) and the corresponding time (Tmax) were derived from the estimated pharmacokinetic parameters (6, 26).

The area under the CSF concentration-time curve from 0 to 24 h (AUC0–24h), which represents CSF exposure to colistin during the 24-hour period, was calculated using the following formula: CMS daily dose/(CL/Fm). The estimated average steady-state concentration (Css) of colistin during 24 h was calculated using the ratio AUC0–24h/24 h. Trough concentration (Ctrough) was the concentration of colistin in CSF measured immediately before dosing. Data were analyzed using a population pharmacokinetic statistical software program (P-Pharm, version 3; Simed, Creteil, France). The population estimation algorithm used in P-PHARM is an expectation-maximization (EM)-type procedure. This algorithm computes the maximum-likelihood estimates by an iterative procedure, as follows: (i) an expectation step (E step), in which the individual parameters are estimated for each individual (Bayesian estimate) given the current population parameters and the individual data, and (ii) a maximization step (M step), in which the population parameters are estimated by maximum likelihood given the current estimates (E step) of the individual parameters. The E and M steps are iterated up to the convergence of the algorithm.

Preliminary analysis revealed that the data were best fitted by a one-compartment model (on the basis of examination of the Akaake criterion, the objective function, and the distribution of residuals), that the probability density function of the random effect parameters was better approximated by a log-normal rather than a normal distribution, and that the distribution of residuals showed that the error variance was better described by a heteroscedastic (proportional to the estimated values of the predictions) model.

**RESULTS**

**Conversion of CMS to colistin in vitro in human CSF.** The conversion of CMS to colistin in human blank CSF was evaluated in vitro by measuring the amount of colistin formed from the hydrolysis of CMS. The percentage of CMS converted to colistin was inversely proportional to the amount of CMS spiked in CSF. At 16 h, the percentages were 101.1, 96.2, 88.1, 62.8, and 35.9 for spiked CMS concentrations of 10, 20, 50, 100, and 200 μg/ml, respectively.

**Potential hydrolysis model.** The potential hydrolysis of CMS was assessed by evaluating the hydrolysis of CMS after incubation of CMS with human CSF. The percentage of CMS converted to colistin was calculated by measuring the amount of colistin formed from the hydrolysis of CMS. The percentage of CMS converted to colistin was inversely proportional to the amount of CMS spiked in CSF. At 16 h, the percentages were 101.1, 96.2, 88.1, 62.8, and 35.9 for spiked CMS concentrations of 10, 20, 50, 100, and 200 μg/ml, respectively.
PK of Intraventricular Colistin

TABLE 2 Estimated pharmacokinetic parameters of colistin in cerebrospinal fluid following intraventricular administration of colistin methanesulfonate at different dose regimens

<table>
<thead>
<tr>
<th>Patient</th>
<th>Dose regimen of CMS (mg)</th>
<th>Daily dose of CMS (mg)</th>
<th>Amt of CSF drained during PK sampling (ml)</th>
<th>Measured C&lt;sub&gt;trough&lt;/sub&gt; (μg/ml)</th>
<th>Estimated pharmacokinetic parameters of colistin in CSF&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C&lt;sub&gt;max&lt;/sub&gt; (μg/ml)</td>
<td>T&lt;sub&gt;max&lt;/sub&gt; (h)</td>
</tr>
<tr>
<td>1</td>
<td>2.61/24 h</td>
<td>2.61</td>
<td>222</td>
<td>0.99</td>
<td>6.2</td>
</tr>
<tr>
<td>2</td>
<td>2.61/12 h</td>
<td>2.61</td>
<td>40</td>
<td>0.8</td>
<td>11.9</td>
</tr>
<tr>
<td>3</td>
<td>2.61/12 h</td>
<td>2.61</td>
<td>55</td>
<td>8.1</td>
<td>10.8</td>
</tr>
<tr>
<td>4</td>
<td>2.61/12 h</td>
<td>2.61</td>
<td>138</td>
<td>2.0</td>
<td>7</td>
</tr>
<tr>
<td>5</td>
<td>5.22/24 h</td>
<td>5.22</td>
<td>148</td>
<td>5.5</td>
<td>22.1</td>
</tr>
<tr>
<td>6</td>
<td>5.22/24 h</td>
<td>5.22</td>
<td>142</td>
<td>6.1</td>
<td>16.2</td>
</tr>
<tr>
<td>7</td>
<td>5.22/24 h</td>
<td>10.44</td>
<td>150</td>
<td>8.4</td>
<td>13.1</td>
</tr>
<tr>
<td>8</td>
<td>5.22/12 h</td>
<td>5.22</td>
<td>300</td>
<td>4.6</td>
<td>9</td>
</tr>
<tr>
<td>9</td>
<td>5.22/12 h</td>
<td>10.44</td>
<td>72</td>
<td>9.7</td>
<td>14.4</td>
</tr>
</tbody>
</table>

<sup>a</sup>The C<sub>trough</sub> values reported here were measured in spontaneously drained CSF.

<sup>b</sup>PK, pharmacokinetics; AUC, area under the CSF concentration-time curve; C<sub>max</sub>, maximum plasma colistin concentration; C<sub>trough</sub>, minimum plasma colistin concentration; C<sub>ss(avg)</sub>, average steady-state concentration; CL/Fm, total CSF clearance of colistin corrected by the unknown fraction (Fm) of CMS converted to colistin; EVD, external ventricular drainage; k<sub>e</sub>, elimination rate constant; k<sub>10</sub>, first-order removal rate constant of colistin from CSF; t<sub>1/2</sub>, elimination half-life; t<sub>1/2a</sub>, terminal half-life of formed colistin; T<sub>max</sub>, time to C<sub>max</sub>; V/Fm, apparent volume of distribution of colistin corrected by Fm.


tively. The AUC<sub>0–16</sub> of colistin formed from the hydrolysis of CMS showed a markedly nonlinear relationship with the amount of spiked CMS (Fig. 1).

CSF concentrations of colistin and population pharmacokinetics analysis. The pharmacokinetics of colistin after IVT administration of CMS could be best described by the one-compartment model (Fig. 2). The values estimated for pharmacokinetic parameters and measured for C<sub>trough</sub> for every patient are detailed in Table 2. The following parameters, reported as means ± SDs, were found to describe colistin CSF disposition in our patients: k<sub>e</sub> = 0.45 ± 0.23 h<sup>−1</sup>, V/Fm = 0.32 ± 0.05 liter, CL/Fm = 0.033 ± 0.014 liter/h, and k<sub>10</sub> = 0.10 ± 0.04 h<sup>−1</sup>. Pharmacokinetic parameters were not influenced by the covariates entered in the model, which were body weight, age, gender, and concomitant intravenous administration of CMS.

The terminal half-life of formed colistin (t<sub>1/2</sub>) was 7.8 ± 3.2 h. The steady-state concentrations (C<sub>ss(avg)</sub>) ranged between 3.0 and 12.2 μg/ml. The average time to C<sub>max</sub> (T<sub>max</sub>) was 3.7 ± 0.9 h.

Figure 3 shows the concentration-time profiles of colistin in CSF at steady state after IVT administration of CMS at different dose regimens. The CSF C<sub>trough</sub> was 0.99 μg/ml when CMS was administered at the dose of 2.61 mg/day, whereas when CMS was administered at doses of ≥5.22 mg/day, C<sub>trough</sub> values were continuously above 2 μg/ml (the accepted MIC value for A. Baumannii, P. aeruginosa, and K. pneumoniae), ranging between 2.0 and 9.7 μg/ml (Table 2).

The values of CSF C<sub>max</sub> and AUC<sub>0–24</sub> increased when the daily dose of CMS was doubled from 2.61 mg to 5.22 mg, but unexpectedly, no further increment was observed when the daily dose of CMS was 10.44 mg.

During the pharmacokinetic sampling period, the amount of CSF drained ranged between 40 and 300 ml (Table 2), and the time of external ventricular drainage closure after CMS administration ranged between 60 and 240 min. A significant (P = 0.0475) correlation was found between the amount of CSF drained and the clearance of formed colistin (CL/Fm) (Fig. 4).

The measured predose concentrations of colistin in CSF at baseline, 24, 48, and 72 h after the day of sampling for pharmacokinetics studies were similar and did not show any statistically significant differences (5.77 ± 2.95, 6.67 ± 4.45, 7.42 ± 4.43, and 5.41 ± 5.13 μg/ml, respectively), indicating that colistin did not accumulate in the CSF in the 3 days which followed sampling for the pharmacokinetics studies.

Assuming a MIC breakpoint of 2 μg/ml, the C<sub>max</sub>/MIC ratio and AUC<sub>0–24</sub>/MIC ratio after a daily dose of CMS of 2.61 mg were 3.1 and 36.2, respectively. After the administration of a daily dose of 5.22 mg, the C<sub>max</sub>/MIC ranged between 3.5 and 11.1 and the AUC<sub>0–24</sub>/MIC ranged between 55.5 and 146.6. After the administration of a daily dose of 10.44 mg, the C<sub>max</sub>/MIC ranged between 4.5 and 7.2 and the AUC<sub>0–24</sub>/MIC ranged between 74.6 and 141.5.

Clinical results. The duration of IVT treatment with CMS ranged between 11 and 36 days (Table 1). Cure of infection (improvement of biochemical parameters and subsequent sterilization of CSF) was observed in 8 of the 9 patients. Four patients died on September 27, 2016 by guest http://aac.asm.org/ Downloaded from
in an intensive care unit; in one patient, death was related to the central nervous system infection. The measured mean creatinine clearance was 114.4 ± 18.6 ml/min (range, 80.2 to 143) before CMS administration and 109.1 ± 15.9 ml/min (range 86.3 to 134) at the end of treatment. None of the patients developed aseptic meningitis or seizures.

DISCUSSION
To our knowledge, this is the first report describing the pharmacokinetics of colistin after IVT administration of CMS. We believed that it was useful to evaluate the pharmacokinetics of colistin for two reasons: (i) the doses and daily regimens of IVT CMS reported in the literature are empirically chosen and very varied (9, 13) and (ii) inflammation of meninges can cause profound alterations in CSF turnover and the efflux of CSF through the external ventricular drainage can vary substantially among patients, which could result in too high (potentially toxic) or too low (subtherapeutic) concentrations of colistin.

Our results show that IVT administration of CMS gives concentrations of colistin that could never be achieved with systemic delivery and confirm that IVT administration of CMS is effective and safe in the treatment of central nervous system infections caused by Gram-negative bacteria susceptible only to colistin.

Assuming a susceptibility breakpoint of 2 μg/ml, the MIC value for A. baumannii, P. aeruginosa, and K. pneumoniae according to the European Committee on Antimicrobial Susceptibility Testing and the U.S. Clinical and Laboratory Standards Institute, when patients were treated with CMS at ≥5.22 mg/day, the CSF concentrations of colistin were continuously above 2 μg/ml, the CL/Fm/MIC ratio was ≥3.5, and the AUC/MIC ratio was ≥55.5. Contrariwise, a daily dose of CMS of 2.61 mg resulted in colistin concentrations which were frequently below 2 μg/ml.

The disappearance of colistin from the CSF was dose independent and monoexponential, with 10% removed every hour. The colistin terminal half-life, which is generally longer for drugs in CSF, was comparable to that reported in plasma (10, 17, 22).

The apparent total CSF clearance of formed colistin (CL/Fm) ranged between 0.018 and 0.058 liter/h (Table 2), showing a large interpatient variability (% coefficient of variation = 42%). Several factors could have contributed to this variability. In fact, CL/Fm results from the unknown fraction of CMS metabolized to colistin (Fm), the diffusion from the CSF to the systemic circulation and the cerebral tissue, and the elimination through the external efflux of CSF. The process of colistin formation from CMS could have been different among patients, but since we only measured colistin (the active antimicrobial agent) and not CMS (the inactive prodrug), we could not evaluate the fraction of CMS converted to colistin and, therefore, its contribution to the variability observed. Second, if we consider that the volume of CSF within the cranial and spinal spaces in an adult is about 150 ml and that the bulk flow is 20 to 30 ml/h (5, 23), another factor which probably played an important role in the disposition and clearance of colistin was the amount of CSF spontaneously drained, which was influenced by the fluctuation of intracranial pressure and ranged between 40 and 300 ml. The correlation between the amount of CSF spontaneously drained and the clearance of colistin (Fig. 4) supports this hypothesis. A better understanding of this factor could have been gained from the measurement of colistin in the CSF collected in the reservoir during the period of sampling (12 or 24 h), but this would have required more frequent sampling to avoid the spontaneous hydrolysis of CMS to colistin, thus increasing the risk of superimposed infections. Another element which is peculiar to patients with a ventriculostomy is the nonuniform time of closure of the external ventricular drainage, both after a drug administration and during the day. This considerable variability (in our patients the range was 60 to 240 min after CMS administration) probably influenced both the clearance of colistin and the amount of formed colistin. Finally, the correlation between the dose of CMS administered intraventricularly and that of CMS converted to colistin by hydrolysis might also have been nonlinear in the infected CSF of our patients (Fig. 1).

For the reasons reported above, the dose-concentration correlation, which in a closed compartment such as CSF should be strong, was in fact weak, and no further increment in values of Cmax and AUC was observed when the dose of CMS was increased to 10.44 mg/day (Fig. 3).

Five of our 9 patients were also treated with intravenous CMS. In these patients, the contribution of intravenous CMS to the concentration of colistin in the CSF is unknown. However, it has been reported that the plasma concentration of colistin is 2 to 3 μg/ml (7, 17, 22, 25), and on the basis of currently available data in humans (1, 11, 21, 30), it is reasonable to expect that diffusion or active transport (active transport has been excluded in an animal model [12]) of colistin across the blood-CSF barrier made a very small contribution to the levels of colistin in the CSF.

Clinical efficacy and toxicity. The IVT administration of CMS was effective in the treatment of the central nervous system infections in our patients. Microbiological cure was obtained in 8 of the 9 patients. In one patient, colistin failed to sterilize the CSF, although the concentrations of the biochemical parameters suggested an improvement of the infection. In one patient, the concomitant administration of fosfomycin could have contributed to CSF sterilization.

Microbiological cure was also obtained in the patient treated with CMS at 2.61 mg/day, even though the concentration of colistin in this patient was often below 2 μg/ml. We believe that it would be unwise to treat patients with central nervous system infections with this dose regimen, given, as well, the marked intraand interpatient variability.

Neurotoxicity (e.g., seizures, aseptic meningitis, hypotonia, diaphragmatic paralysis, and cauda equine syndrome) has been described after systemic or IVT/intrathecal administration of colis-
tin (9, 14, 15, 24). At the doses used in our patients, we did not observe signs or symptoms of central nervous system toxicity, but our patients were mechanically ventilated and sedated, and therefore, we might have underestimated this aspect.

Conclusions. IVT administration of CMS gives concentrations of colistin in CSF that could never be achieved with systemic delivery. IVT administration of CMS at doses of ≥5.22 mg/day was appropriate for the treatment of central nervous system infections caused by pan-resistant Gram-negative bacteria in our patients, but since several factors can influence the clearance of colistin and its concentrations in CSF (in particular, the external drainage of CSF), the daily dose of 10 mg suggested by the Infectious Diseases Society of America may be more prudent.

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