Penetration of Colistin into Cerebrospinal Fluid[▽]

S. L. Markantonis,^{1*} N. Markou,² M. Fousteri,¹ N. Sakellaridis,³ S. Karatzas,⁴
I. Alamanos,² E. Dimopoulou,² and G. Baltopoulos⁴

*University of Athens, Faculty of Pharmacy, Laboratory of Biopharmaceutics and Pharmacokinetics, 157.71 Athens, Greece¹;
ICU-B, KAT Hospital, 2 Nikis Str. Kifissia, 145.61 Athens, Greece²; Department of Neurosurgery,
KAT Hospital, 2 Nikis Str. Kifissia, 145.61 Athens, Greece³; and University of Athens School of
Nursing ICU, KAT Hospital, 2 Nikis Str. Kifissia, 145.61 Athens, Greece⁴*

Received 13 March 2009/Returned for modification 31 May 2009/Accepted 3 August 2009

Colistin penetration into the cerebrospinal fluid (CSF) was studied in five critically ill adult patients receiving colistin methanesulfonate for infections by multiresistant gram-negative bacilli. Colistin concentrations were determined in paired serum and CSF samples, with the latter taken by lumbar puncture, with the exception of one patient with an external ventriculostomy. CSF-to-serum ratios (0.051 to 0.057) for all study patients coincided at all sampling times. The low level (5%) of penetration suggests inadequate bactericidal colistin concentrations in the CSF.

Several case reports have described the successful treatment of central nervous system (CNS) infections with colistin (in the form of colistin methanesulfonate [CMS]) administered intravenously and/or either intrathecally or intraventricularly (2, 7–11, 16). However, initial data derived from colistin concentrations measured by microbiological assay suggested poor drug penetration into the cerebrospinal fluid (CSF), which was not enhanced in the presence of meningeal inflammation (5), while more recently, a 25% peak CSF-to-serum concentration ratio (8) and a ~15% ratio of areas under the CSF/serum concentration-time profiles were reported (9). These findings raise concerns about the effectiveness of intravenous (i.v.) CMS monotherapy. Furthermore, as the data (5, 8, 9) relating to the penetration of colistin into the CSF are based solely on unreliable bioassay measurements, these have to be confirmed by high-performance liquid chromatography, which is now considered to be the only valid approach for quantifying colistin levels (12).

In order to determine the CSF penetration of colistin after i.v. administration of CMS, we performed a prospective study of five nonconsecutive critically ill adult patients treated with i.v. CMS for serious gram-negative infections (not necessarily CNS infections) (Table 1). All patients had CSF withdrawn either for diagnostic reasons (suspected meningitis or ventriculitis) or for the follow-up of a documented CSF infection. The study was approved by the Hospital Ethics and Research Committee and performed in accordance with good clinical practice guidelines. Informed consent was waived.

CMS (colistin; Norma, Athens, Greece) was administered intravenously (100-ml infusion over 30 min). The dosage regimen varied, at the discretion of the attending physician (Table 2). Samples were collected after at least 2 days of CMS administration, allowing colistin concentrations to reach steady

state (with the exception of patient 5 who had rapidly deteriorating renal function). CSF sampling was performed through lumbar puncture, with the exception of patient 1 who had CSF withdrawn through a preexisting external ventriculostomy for hydrocephalus drainage. For patient 1, CSF/serum samples were collected before CMS infusion and at 10 min, 1 h, 2 h, 4 h, 6 h, and 8 h after the end of CMS infusion, while for patients 2, 3, 4, and 5, paired samples were collected at two time points (Table 2). All samples were immediately transferred on ice to the laboratory, cold centrifuged without delay ($1,000 \times g$, 10 min), and stored at -70°C until analysis by an isocratic high-performance liquid chromatography assay, as previously reported (14). The assay response was linear, between 500 and 5,000 ng/ml for colistin sulfate in sera and between 40 and 1,000 ng/ml in CSF. On a daily basis for the needs of the specific research protocol, the calibration range used for sera was 500 to 2,000 ng/ml and for CSF was 40 to 200 ng/ml. Validation studies included determination of precision, accuracy, and recovery. For the 500-, 1,000-, and 2,000-ng/ml concentrations, intraday and interday variabilities for sera were 6.3, 5.0, and 2.2% and 8.0, 3.8, and 2.9%, respectively, while for the 40-, 80-, and 200-ng/ml concentrations, intraday and interday variabilities for CSF were 5.5, 5.3, and 4.3% and 8.7, 6.2, and 4.9%, respectively. The lower limits of quantification were 80 ng/ml for sera and 40 ng/ml for CSF.

The pharmacokinetic parameters of colistin in sera and CSF were estimated from the concentration-time data of patient 1 by noncompartmental, steady-state analysis using the WinNonlin pharmacokinetic software package (Pharsight Corporation, Mountain View, CA).

Characteristics of the patients investigated are presented in Table 1. Patients 1 and 2 had CNS infections (ventriculitis) from *Acinetobacter baumannii*, while patient 3 had a CNS infection from vancomycin-resistant enterococcus. Patient 2 had received intrathecal colistin, but the last dose had been administered 4 days before CSF sampling, and we assume it did not influence our measurements. On the basis of CSF examination, all three patients with CNS infection had minimal CSF inflammation at the time of sampling. Data on the administered CMS

* Corresponding author. Mailing address: Department of Pharmaceutical Technology, Laboratory of Biopharmaceutics and Pharmacokinetics, Faculty of Pharmacy, University of Athens, Panepistimiopolis, 157.71 Athens, Greece. Phone: 30-210-7274676. Fax: 30-210-7274027. E-mail: kyroudi@pharm.uoa.gr.

[▽] Published ahead of print on 24 August 2009.

TABLE 1. Characteristics of the patients investigated^a

Patient no.	Sex	Age (yr)	Reason for ICU admission	Weight (kg)	Serum creatinine (mg/dl)	Infection/pathogen treated with CMS	Other antibiotics administered	Outcome
1	F	40	Head injury	81	0.5	Ventriculitis/ <i>A. baumannii</i>	Tigecycline	Response, sterilization, survival
2	F	68	Head injury	67	1.1	Ventriculitis/ <i>A. baumannii</i>	Meropenem	Response, sterilization, death unrelated to infection
3	M	62	SAH, intraventricular hemorrhage	68	0.6	VAP/ <i>A. baumannii</i>	Meropenem, linezolid	Death unrelated to infection
4	M	36	Intracerebral hemorrhage	80	0.8	VAP/ <i>A. baumannii</i>	Meropenem	Response, survival
5	M	60	SAH	74	Anuric, CVVHDF	BSI/ <i>A. baumannii</i>	Meropenem	No response, death

^a F, female; M, male; ICU, intensive care unit; VAP, ventilator-associated pneumonia; SAH, subarachnoid hemorrhage; BSI, bloodstream infection; CVVHDF, continuous venovenous hemodiafiltration.

TABLE 2. Details of CMS dosage, sampling times of biological fluids, and concentrations of colistin in sera and in CSF after i.v. administration

Patient no.	CMS regimen (mg/day)	Day of CMS treatment	Time of sampling ^a	Colistin concn (ng/ml)		Colistin ratio (CSF/sera)
				CSF	Sera	
1	225/3	12	1 h	83	1,548	0.054
2	225/3	12	2 h	97	1,810	0.054
		14	1 h	99	1,920	0.052
3	150/2	6	2 h	43	819	0.053
		10	3 h	41	802	0.051
4	225/3	6	1 h	83	1,551	0.054
		5	Trough	42	820	0.051
5	150/1	8	1 h	88	1,534	0.057
		8	Trough	48	871	0.055

^a Trough, drug concentration measured just before the administration of the next dose.

regimen and CSF penetration are presented in Table 2. The concentration-time curves depicting the colistin serum and CSF data of patient 1 are shown in Fig. 1, and the estimated pharmacokinetic parameters are shown in Table 3. The ratio of the area under the concentration-time curve (AUC) for CSF to that of sera (AUC_{CSF}/AUC_S) was 0.051.

In patient 1, the concentration-time curves of colistin in sera and CSF ran parallel (with a CSF-to-serum ratio of ~ 0.05 at all time points, coinciding with a AUC_{CSF}/AUC_S ratio of 0.051 [Table 3]), the time to peak levels were the same, and the elimination half-lives were similar in the two biological fluids, in contrast to most other antibiotics, where CSF concentration-time curves usually lag behind those in sera because of their slow entry through the blood-brain barrier (1, 4, 13, 15). However, since the lack of lag time was based on the determination of colistin concentrations in only one patient, this finding needs to be confirmed using a larger number of patients. The ratios of CSF-to-serum concentrations for the five study patients coincided in all cases, despite widely different sampling times, suggesting that the elimination half-lives of colistin in the CSF and sera were similar. Furthermore, in all five patients, the ratios at steady state were equal to the AUC_{CSF}/AUC_S ratio of patient 1, indicating that colistin exchange between the central compartment and the CSF is governed by first-order kinetic processes (15).

The main finding of our study is that colistin has a CSF penetration of only 5%. This is even less than that shown in previously reported data, based on colistin concentrations determined by bioassay (8, 9). From what we know about colistin pharmacodynamics (6, 12), the levels of colistin measured in the CSF in our study are unlikely to be effective for the eradication of gram-negative bacilli from the CNS. The favorable response of patient 1 could probably be attributed to the co-administration of i.v. tigecycline and, in patient 2, to intrathecal colistin plus i.v. meropenem.

Another finding of interest is that no difference in colistin penetration was found between patients with CNS infection (albeit without intense meningeal inflammation [3]) and those without. Indeed, all study patients had minimally inflamed meninges on the day of sampling; therefore, we cannot rule out the possibility that colistin levels in CSF may be higher in

FIG. 1. Colistin serum and CSF concentrations (ng/ml) versus time profiles under steady-state conditions after three 225-mg doses of CMS in patient 1.

patients with bacterial meningitis and intense meningeal inflammation.

It is not easy to provide an adequate explanation for the low level of penetration of colistin in the CSF and the corresponding kinetics of this drug in CSF and sera. The very high molecular weight of the drug probably contributes, as it is known that at least for hydrophilic molecules, the rate of diffusion of a molecule into the CSF is inversely proportional to its size (1, 4, 15). The extent of protein binding of colistin (~60% in a rat animal model [12]) is not expected to affect CSF penetration, while precise data on colistin lipophilicity remain unknown.

The shortcomings of our study are that no patient in our series had intense meningeal inflammation and that full concentration-time curves were available only for one patient. Nevertheless, the similar CSF-to-serum concentration ratios at steady state estimated in our study, regardless of sampling

time, allow us to be confident that for colistin, even single determinations in CSF and serum samples can provide reliable information on CSF penetration of colistin.

Thus, we conclude that colistin penetration to the CSF is very low (~5%), at least in patients without intense meningeal inflammation. On the basis of this finding, concomitant intrathecal administration of colistin seems warranted for the treatment of CNS infections from gram-negative bacilli.

REFERENCES

- Andes, D. R., and W. A. Craig. 1999. Pharmacokinetics and pharmacodynamics of antibiotics in meningitis. *Infect. Dis. Clin. N. Am.* **13**:595–618.
- Benifla, M., G. Zucker, A. Cohen, and M. Alkan. 2004. Successful treatment of *Acinetobacter* meningitis with intrathecal polymyxin E. *J. Antimicrob. Chemother.* **54**:290–292.
- Brown, E. M. 2007. Neurosurgical infections in intensive care unit patients, p. 580–594. *In* J. Rello, M. Kollef, E. Diaz, and A. Rodriguez (ed.), *Infectious diseases in critical care*, 2nd ed. Springer Publishing Company, New York, NY.
- de Lange, E. C., and M. Danhof. 2002. Considerations in the use of cerebrospinal fluid pharmacokinetics to predict brain target concentrations in the clinical setting. *Clin. Pharmacokinet.* **41**:691–703.
- Everett, E. D., and L. J. Strausbaugh. 1980. Antimicrobial agents and the central nervous system. *Neurosurgery* **6**:691–714.
- Falagas, M. E., and S. K. Kasiakou. 2005. Colistin: the revival of polymyxins for the management of multidrug-resistant Gram-negative bacterial infections. *Clin. Infect. Dis.* **40**:1333–1341.
- Fernandez-Viladrich, P., X. Corbella, L. Corral, F. Tubau, and A. Mateu. 1999. Successful treatment of ventriculitis due to carbapenem-resistant *Acinetobacter baumannii* with intraventricular colistin sulfomethate sodium. *Clin. Infect. Dis.* **28**:916–917.
- Jimenez-Mejias, M. E., B. Becerril, F. J. Marquez-Rivas, C. Pichardo, L. Cuberos, and J. Pachon. 2000. Successful treatment of multidrug-resistant *Acinetobacter baumannii* meningitis with intravenous colistin sulfomethate sodium. *Eur. J. Clin. Microbiol. Infect. Dis.* **18**:970–971.
- Jimenez-Mejias, M. E., C. Pichardo-Guerrero, F. J. Marquez-Rivas, D. Martin-Lozano, T. Prados, and J. Pachon. 2002. Cerebrospinal fluid penetration and pharmacokinetic/pharmacodynamic parameters of intravenously administered colistin in a case of multidrug-resistant *Acinetobacter baumannii* meningitis. *Eur. J. Clin. Microbiol. Infect. Dis.* **21**:212–214.
- Kasiakou, S. K., P. I. Rafailidis, K. Liaropoulos, and M. E. Falagas. 2005. Cure of post-traumatic recurrent multidrug-resistant gram-negative rod meningitis with intraventricular colistin. *J. Infect.* **50**:348–352.
- Levin, A. S., A. A. Barone, J. Penco, M. V. Santos, I. S. Marinho, E. A. G.

TABLE 3. Pharmacokinetic parameters of colistin estimated from serum and CSF concentrations at steady state after i.v. administration of CMS in patient 1

Type of sample	Pharmacokinetic parameters of colistin ^a					
	C_{max} (ng/ml)	C_{min} (ng/ml)	$t_{1/2}$ (h)	CL_{ss} (liter/h)	V_{ss} (liters)	AUC (h · mg/liter)
Sera	1,679.3	925.6	11.1	15.2	238	10.4
CSF	90.0	47.3	11.7			0.53

^a C_{max} , colistin concentration 10 min after the end of the infusion; C_{min} , drug concentration at 8 h; $t_{1/2}$, elimination half-life; CL_{ss} , apparent clearance at steady state calculated as dose/AUC; V_{ss} , apparent volume of distribution at steady state calculated as mean residence time × CL_{ss} . For the pharmacokinetic evaluations, the CMS dose was corrected to an equivalent dose of colistin, according to the molecular weight of the two major components, i.e., CMS dose × 1,163/1,743, or CMS dose × 0.667, where 1,163 is the average molecular weight of colistin A and B and 1,743 is the average molecular weight of the respective sodium methane-sulfonate salts. Since the precise percentage of colistin A and B, in the batch of CMS administered, was unknown, the precise dose of colistin base could not be estimated with greater accuracy.

- Arruda, E. I. Manrique, and S. F. Costa. 1999. Intravenous colistin as therapy for nosocomial infections caused by multidrug resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. *Clin. Infect. Dis.* **28**:1008–1011.
12. Li, J., R. L. Nation, J. D. Turnidge, R. W. Milne, K. Coulthard, C. R. Rayner, and D. L. Paterson. 2006. Colistin: the re-emerging antibiotic for multidrug-resistant Gram-negative bacterial infections. *Lancet Infect. Dis.* **6**:589–601.
13. Lutsar, I., G. H. McCracken, Jr., and I. R. Friedland. 1998. Antibiotic pharmacodynamics in cerebrospinal fluid. *Clin. Infect. Dis.* **27**:1117–1129.
14. Markou, N., S. L. Markantonis, E. Dimitrakis, D. Panidis, E. Boutzouka, S. Karatzas, P. Rafailidis, H. Apostolakis, and G. Baltopoulos. 2008. Colistin serum concentrations after intravenous administration in critically ill patients with serious multi-drug resistant, Gram-negative bacilli infections: a prospective, open label, uncontrolled study. *Clin. Ther.* **30**:143–151.
15. Nau, R., F. Sorgel, and H. W. Prange. 1998. Pharmacokinetic optimization of the treatment of bacterial central nervous system infections. *Clin. Pharmacokinet.* **35**:223–246.
16. Vasen, W., P. Desmery, S. Ilutovich, and A. Di Martino. 2000. Intrathecal use of colistin. *J. Clin. Microbiol.* **38**:3523.