PENETRATION OF COLISTIN INTO CENTRAL NERVOUS SYSTEM IN CRITICALLY ILL PATIENTS WITH PROVEN OR SUSPECTED CENTRAL NERVOUS SYSTEM INFECTIONS

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INTRODUCTION AND PURPOSE

Colistin has been used for the treatment of central nervous system infections (CNS) caused by multi-drug resistant gram-negative bacteria (MDR-GNB) but the information about its pharmacokinetics and penetration into the cerebrospinal fluid (CSF) is very limited. The objective was to assess the penetration of colistin into the CNS in patients treated with colistimethate sodium (CMS) for a proven or suspected CNS infections caused by MDR-GNB.

METHODS

Pharmacokinetic study including 3 critically ill patients treated with intravenous CMS for a proven or suspected CNS infection caused by MDR-GNB. Data collected: demographics, clinical and pharmacokinetics. Colistin levels were measured at steady state at different times points, $Cmin_{ss}$ or trough (pre-dose) and $Cmax_{ss}$ or peak (30 minutes after the end of the 30-min infusion of CMS) in plasma and CSF and were analysed by a validated HPLC method. All patients were undergoing an external ventricular drainage (EVD) or an external lumbar drainage (ELV).

RESULTS

Table 1: Clinical and pharmacokinetic data of the included patients

Variable	Patient 1	Patient 2	Patient 3
Gender	Male	Female	Female
Age (years)	73	55	48
APACHE-II	18	24	18
Diagnosis at ICU admisión	Suprarenal insufficiency	Subaracnoid haemorrhage	Cerebellar haematoma
CMS treatment	Empirical	Directed	Directed
CNS infection	Suspected CNS infected by a MDR-*Pseudomonas aeruginosa*	Ventriculitis caused by a MDR-*Acinetobacter baumannii*	Ventriculitis and meningitis caused by MDR- *Pseudomonas aeruginosa*
CMS daily doses (MUI)	2 MUI/8h	2 MUI/8h	3 MUI/8h
Colistin base activity daily dose (mg)	200	200	300
MIC to colistin (mg/L)	-	-	0.25
Other concomitant antibiotics	Linezolid	Tygeciclin	Ciprofloxacin
Intravenous corticoids	Hydrocortisone	No	No
Clinical data at the day of sample extraction			
GFR (mL/min/1,73 m^2)	180.9	254	225.5
Serum albumin (g/dl)	2.9	2.7	3.4
Vasopressors	Yes (Noradrenalin)	No	No
Colistin plasma concentrations			
$Cmin_{ss}$ (mg/L)	2.4	-	0.5
$Cmax_{ss}$ (mg/L)	2.1	1	0.6
Colistin concentrations in CSF			
$Cmin_{ss}$ (mg/L)	-	-	0.2
$Cmax_{ss}$ (mg/L)	<0.1	<0.1	0.2
Ratio CSF/plasma concentration			
$Cmin_{ss}$ (mg/L)	-	-	0.4
$Cmax_{ss}$ (mg/L)	<0.05	<0.1	0.3
Extraction method of CSF sample	Lumbar puncture	ELV	EVD
Exitus	No	No	No

ICU: Intensive Care Unit, CNS: central nervous system, CMS: colistimethate sodium, MIC: minimum inhibitory concentration, GFR: glomerular filtration rate calculated by MDRD-6, Cminss: minimum concentration in steady state, Cmaxss: maximum concentration in steady state, MDR: multi-drug resistant, CSF: cerebrospinal fluid, ELV: external lumbar drainage, EVD: external ventricular drainage.

CONCLUSIONS

- In two patients, the concentration of colistin in cerebrospinal fluid was undetectable and in the third one the level was lower than the minimum inhibitory concentration of colistin against the isolated multi-drug resistant Pseudomonas aeruginosa.
- A higher ratio of cerebrospinal fluid/plasma colistin concentration was observed in the patient in whose cerebrospinal fluid samples were obtained through an external ventricular drainage.
- A better knowledge of the clinicall and methodologicall factors influencing the penetration of this polymyxin into central nervous system is urgently needed.
- Until then, these findings suggest the use of intrathecal colistimethate sodium for the treatment of central nervous system infections caused by multi-drug resistant gram-negative bacteria and also the need to monitor colistin levels in the central nervous system to avoid treatment failure due to suboptimal exposure.