P1727
Poster Session VI
PK/PD of antibiotics against Gram-negatives

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

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ObjectivesColistin 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 ($Cmin^{ss}$ or trough (pre-dose), and $Cmax^{ss}$ (30 minutes after the end of the 30-min infusion of CMS) in plasma and cerebrospinal fluid (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

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 in a patient infected by a MDR-*P. aeruginosa*	Ventriculitis caused by a MDR-*A.baumannii*	Ventriculitis and meningitis caused by MDR- *P.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

* GFR: glomerular filtration rate calculated by MDRD-6

Conclusions

· In two patients, the concentration of colistin in CSF was undetectable and in the third one the level was lower than the MIC of the isolated MDR-*P.aeruginosa*.

· A higher ratio CSF/plasma concentration colistin was observed in the patient in whom the CSF samples were obtained through an EVD.

· A better knowledge of the clinically and methodologically factors influencing the penetration of this polymyxin into CNS is urgently needed.

· Until then, these findings suggest the use of intrathecal colistin for the treatment of CNS infections caused by MDR-GNB and also the need to monitoring colistin levels in the CNS to avoid treatment failure due to suboptimal exposure.