Urinary concentrations of colistimethate sodium (CMS) and formed colistin in patients with multidrug-resistant gram-negative bacterial (MDR-GNB) infections after intravenous administration

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Objectives

Colistin is widely used for treatment of urinary tract infections (UTIs) caused by multidrug-resistant gram-negative bacteria (MDR-GNB); however, little information is available on its urinary excretion in infected patients. This study aimed to investigate the pharmacokinetics of colistimethate sodium (CMS) and formed colistin in urine in patients with MDR-GNB infections.

Methods

A pharmacokinetic study was conducted in 9 patients with MDR-GNB infections treated with CMS in a university hospital from January to August 2014. Demographics, CMS dose (selected by the physician), estimated glomerular filtration rate (eGFR) at start and end of CMS therapy, concentration of CMS and formed colistin in urine, volume of urine, and co-administered nephrotoxic drugs were recorded. A urine sample was collected in each patient prior to CMS administration and over 0-2, 2-4 and 4-6 h. Blood samples were obtained pre-dose ($Cmin_{ss}$) and end of infusion ($Cmax_{ss}$) at steady state for measurement of concentrations of CMS and formed colistin using HPLC. CMS urinary recovery was determined as the summed amount of CMS and formed colistin recovered in urine for each 2-h interval divided by the CMS dose. Quantitative variables were expressed as median (interquartile range) and Spearman test was employed for bivariate correlations.

Results

In the enrolled 9 patients: 7 (77.8%) male, age: 65 (63-70) years; $Cmin_{ss}$ and $Cmax_{ss}$ of CMS in plasma: 4.1 (1.9-4.6) and 10.4 (4.7-11.7) mg/L, respectively; eight patients (88.9%) received nephrotoxic drugs (7 furosemide and 3 vancomycin, being the most common).

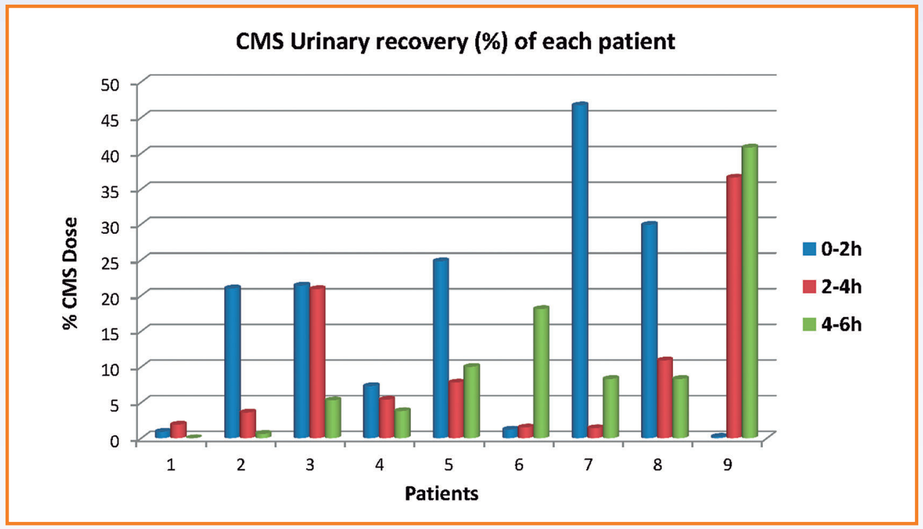
Clinical and PK data are shown in the Table 1.

Table 1. Clinical and pharmacokinetic characteristics of the included patients

Pt.	CMS administered dose	Initial eGFR (mL/min)*	Final eGFR (mL/min)*	Colistin $Cmin_{ss}$ in plasma (mg/L)	Range of concentrations in urine (mg/L)	
					Colistin	CMS
1	1MUI/24h	9	7	0.8	0.5-1.7	3.2-18.9
2	1MUI/8h	266	156	1.5	<0.1-0.6	1.5-64.8
3	1MIU/8h	56	52	0.4	3.2-12.5	37.3-139.2
4	2MUI/12h	49	56	0.9	1.8-4.8	11.1-67.3
5	2MIU/8h	85	108	1.4	9.3-25.9	105.4-362
6	2MIU/8h	93	38	0.8	4.5-15.8	58-211.3
7	3MIU/8h	190	332	0.7	1.9-23.9	78.3-491.4
8	3MUI/8h	122	58	0.9	8.5-21.3	58.7-194.1
9	4.5MIU/12h	136	114	1.4	3.2-95.4	9.2-1699.6

*MDRD-4 equation; **Collected in 4h

Graph 1. CMS Urinary recovery of the included patients



CMS urinary recovery 0-6h showed a tendency to be positively correlated with the initial eGFR (rho:0.633; p:0.067).

Conclusions

- This is the first study to examine the urinary recovery of CMS in patients with a 2-h interval. Concentrations of formed colistin were higher than those in plasma and also above the MIC value (0.5 mg/L) of the most predominant strain of *Pseudomonas aeruginosa* in our hospital.
- Future studies are warranted for optimising CMS dosage regimens in patients with UTI.

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