Colistin distribution into the peritoneal fluid of a patient with severe peritonitis

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Key-words: colistin, pharmacokinetics, nosocomial infection, peritonitis
Colistin appears more and more frequently as a last line defense therapy against nosocomial infections due to multi-resistant Gram-negative bacteria (8). For parenteral administration, colistin is used as a prodrug, colistin methanesulfonate or CMS, which is less toxic but inactive and hydrolyzed in vivo into colistin. Its pharmacokinetics is complex but better understood since recently (1, 2, 4, 9). Yet although peritonitis is the second cause of lethal infections in critical care patients (10), colistin distribution in patients peritoneal fluid (PF) has never been described.

An 85-year old man weighting 69 kg underwent surgical resection to remove colon carcinoma. His creatinine clearance (CL\textsubscript{crea}) was stable at 35 mL/min. On Day 4 post-surgery, he developed intra-abdominal infection requiring further surgery and drainage of the abdominal cavity. Antibiotic therapy was started with a combination of piperacillin-tazobactam and amikacin. *Escherichia coli* and *Pseudomonas aeruginosa* were isolated from the abdominal cavity and amikacin was switched to colistin. CMS was given intravenously over 60-min, starting with an initial loading dose of 8 millions international units (MIU) corresponding to 640 mg of CMS. A maintenance dose was selected according to Eq. 1, with a target colistin plasma concentration ranging between 2 and 4 µg/mL (2).

\[ C_{SS,avg} = \frac{CL_{NR} \times Dose}{CL_{R} + CL_{NR} \times \tau \times CL_{coli}} \]  

Eq. 1

For these calculations CMS renal clearance (CL\textsubscript{R}) was set at 0.85 CL\textsubscript{crea}, CMS non-renal clearance (CL\textsubscript{NR}) was considered equal to 27 mL/min and colistin clearance (CL\textsubscript{coli}) to 35 mL/min, as previously estimated in critical care patients (6). Accordingly a maintenance dose equal to 2 MIU/8h was selected, corresponding to a predicted average plasma colistin concentration at steady-state (C\textsubscript{SS,avg}) equal to 3.0 µg/mL. Plasma and PF samples were rapidly
frozen at -80°C pending assay. CMS and colistin concentrations were measured in plasma and
PF after the loading dose and at steady-state (after the 7th dose) by liquid chromatography-
tandem mass spectrometry (5).

CMS peak concentration in plasma obtained after the loading dose (59 µg/ml) was
about 3-fold higher than after the maintenance dose at steady-state (18 µg/ml). Corresponding
peak concentrations in PF were much lower (3.7 µg/ml and 0.8 µg/ml respectively) which
may be due to a slow distribution and/or rapid conversion of CMS in colistin within PF.
Following the CMS loading dose, colistin concentrations increased more slowly in PF than in
plasma, attesting for relatively slow distribution (Fig. 1a), but at steady-state colistin PF
concentrations compared favorably with plasma concentrations, which were close to values
predicted from Eq. 1 (Fig. 1b). By comparison concentrations of carbapenem (3,7) were
shown to be much lower in PF than in plasma due to peripheral degradation in patients with
peritonitis. Noticeably precise characterization of CMS and colistin PF distribution, as well as
colistin antimicrobial activity, should ideally rely on unbound concentrations which are
unfortunately almost impossible to determine in practice when both compounds are present in
the medium. Yet this case report suggests that colistin presents pharmacokinetic
characteristics, in particular chemical stability, in favor of its use for the treatment of
peritonitis.
Figure 1: Plasma (●) and PF (○) colistin concentrations measured in a patient with peritonitis: (a) after an initial 8 MIU CMS loading dose and (b) at steady-state following multiple CMS administrations at 2 MIU every 8 hours.

Financial support:

This work was supported in part by a grant from National Ministry of Health (PHRC National 2009).


