Pulmonary disposition of Polymyxins

William Couet, PharmD, PhD

2 May 2013
Optimal characteristics of antibiotics for nebulization

Alveolar space

Low permeability

Epithelial Lining Fluid

Pneumocyte

Macrophage

Efflux transport
1- Pre-clinical experiments
Effect of route of administration on colistin ELF concentrations

Colistin administration

IV infusion (~ 0.35mg/kg, 30min) (n=6)

Nebulization (100µL, ~ 0.35mg/kg) (n=6)

Blood collection by intracardiac puncture

BAL collection (1mL NaCl 0.9%, 37°C)

MicroSprayer IA-1B system

LC-MS/MS assay (Gobin et al. AAC, 2010)
Effect of route of administration on colistin ELF concentrations

ELF concentrations strongly depend upon the route of administration.

- **IV administration**
  - Concentrations (µg/mL)
  - Time (h)

- **Nebulization**
  - Concentrations (µg/mL)
  - Time (h)

**Legend:**
- Red circles: plasma
- Blue dashed line: ELF
CMS disposition after nebulization in rats

1- Fraction of the CMS dose converted pre-absorption

(Marchand S. et al., AAC, 2010)
CMS disposition after nebulization in rats

2- Colistin ELF concentrations

Nebulization

PK

CMS

ELF

Formation rate

Absorption rate

(Marchand S. et al., AAC, 2010)
CMS and Colistin concentrations in ELF
(CMS 15 mg/Kg nebulized in rats)

(Marchand S. et al., AAC, 2010)
2- Clinical experiments

2.1 Critical Care patients
Steady-State Pharmacokinetics and BAL Concentration of Colistin in Critically III Patients After IV Colistin Methanesulfonate Administration

Roberto Imberti, MD; Maria Cusato, PharmD; Paola Villani, BiolD; Livio Carnevale, MD; Giorgio A. Iotti, MD; Martin Langer, MD; and Mario Regazzi, PharmD

Background: Infections caused by multidrug-resistant gram-negative bacteria have caused a resurgence of interest in colistin. To date, information about pharmacokinetics of colistin is very limited in critically ill patients, and no attempts have been made to evaluate its concentration in BAL.

Methods: In this prospective, open-label study, 13 adult patients with ventilator-associated pneumonia caused by gram-negative bacteria were treated with colistin methanesulfonate (CMS) IV, 2 million International Units (174 mg) q8h, a usually recommended dose, for at least 2 days. Blood samples were collected from each patient at time intervals after the end of infusion. BAL was performed at 2 h. Colistin was measured by a selective, sensitive high-performance liquid chromatography-based method. Pharmacokinetic parameters were determined by noncompartmental analysis.

Results: Patients received 2.19 ± 0.38 mg/kg (range, 1.58-3.16) of CMS per dose. At steady state, mean ± SD plasma colistin maximum (Cmax) and trough (Ctrough) concentrations were 2.21 ± 1.08 and 1.03 ± 0.69 μg/mL, respectively. Mean ± SD area under the plasma concentration-time curve from 0 to 8 h (AUC₀₈), apparent elimination half-life, and apparent volume of distribution were 11.5 ± 6.2 μg × h/mL, 5.9 ± 2.6 h, and 1.5 ± 1.1 L/kg, respectively. Cmax/minimum inhibitory concentration (MIC) ratio and AUC₀₈/MIC ratio (MIC = 2 μg/mL) were 1.1 ± 0.5 and 17.3 ± 9.3, respectively. Colistin was undetectable in BAL. Nephrotoxicity was not observed.

Conclusions: Although the pharmacodynamic parameters that better predict the efficacy of colistin are not known in humans, in critically ill adult patients the IV administration of CMS 2 million International Units (174 mg) q8h results in apparently suboptimal plasma concentrations of colistin, which is undetectable in BAL. A better understanding of the pharmacokinetic-pharmacodynamic relationship of colistin is urgently needed to determine the optimal dosing regimen.
Pharmacokinetics of inhaled colistimethate sodium (CMS) in mechanically ventilated critically ill patients

CMS (1 MIU) nebulization in patients (n=20)
PK study in Critical Care Patients

- Patients: n=12, 54±19 y, CrCL: 134±53 ml/min
- CMS dosing: 2 MIU IV or Nebulized (30 min)
- Sampling: Blood (n= 276) and mini-BAL (n=48)
- Assay: CMS and colistin in plasma and BAL by LC-MS/MS
- PK analysis: simultaneous analysis (S-ADAPT): of CMS and colistin in plasma and ELF after IV infusion & Nebulization
Effect of route of administration

1- on colistin plasma concentrations
Effect of route of administration

2- on colistin ELF concentrations

![Graph showing ELF concentrations over time for IV and Neb routes of administration.](image)
Modeling results

\[ F_{\text{areo}} = 11\% \]

- **BAL CMS**
  - \( V_{\text{BAL}} = 1.8 \text{mL} \)
  - \( \text{CL}_{\text{CMS-Coli,BAL}} = 7.8 \mu\text{L/min} \)
  - \( \text{CL}_{\text{out,CMS}} = 14.7 \mu\text{L/min} \)
  - \( \text{CL}_{\text{in,CMS}} = 11.7 \mu\text{L/min} \)
- **BAL colistin**
  - \( V_{\text{BAL}} = 1.8 \text{mL} \)
  - \( \text{CL}_{\text{out,Coli}} = 19.9 \mu\text{L/min} \)
  - \( \text{CL}_{\text{in,Coli}} = 15.7 \mu\text{L/min} \)
- **Plasma CMS**
  - \( V_{\text{CMS}} = 14 \text{L} \)
  - \( \text{CL}_{\text{ER,CMS}} = 34.8 \text{mL/min} \)
  - \( \text{CL}_{\text{R,CMS}} = 77.2 \text{mL/min} \)
- **Plasma colistin**
  - \( V_{\text{coli}} = 23.7 \text{L} \)
  - \( \text{CL}_{\text{coli}} = 82.0 \text{mL/min} \)
Typical fit
Predicted effect of colistin within ELF after Aerosol vs IV administration of CMS

**Kill Curve Experiment**

- **S**
  - $K_{max} = 3.3 \, h^{-1}$
  - $K_{50S} = 0.70 \, mg/L$

- **R**
  - $K_{max} = 3.3 \, h^{-1}$
  - $K_{50R} = 25 \, mg/L$

$K_G = 0.76 \, h^{-1}$

**Fig. 6:** Predicted bacterial count over time following dosing with 2 MIU of CMS IV (left) or nebulized (right)
2- Clinical experiments

2.1 Cystic Fibrosis patients
Comment on: Pharmacokinetics of inhaled colistin in patients with cystic fibrosis

Jian Li* and Roger L. Nation

Sir,

Ratjen et al. recently published an important paper in JAC reporting the pharmacokinetics of colistin after inhalation of colistin methanesulphonate in patients with cystic fibrosis.

In summary, Ratjen et al. provided some potentially useful information on the pharmacokinetics of colistin after inhalation of colistin methanesulphonate. However, because of lack of clarity regarding the quantification of colistin in biological fluids and the pharmacokinetic analysis, caution is required when these data are used as reference for inhalation therapy of colistin methanesulphonate in CF patients.
2. PK study in Cystic Fibrosis Patients

- Patients: n=4, females, 21-32 years, 37-65 Kg

- CMS dosing: 2 MIU IV or Nebulized (10 min)

- Sampling: Blood (n= 80) and Expectorations (n=12)

- Assay: CMS and colistin in plasma and BAL by LC-MS/MS

- PK analysis: simultaneous analysis (S-ADAPT):
  - of CMS and colistin
  - in plasma and sputum
  - after IV infusion & Nebulization
Effect of route of administration

1- on colistin plasma concentrations
Effect of route of administration

2- on colistin Sputum concentrations

![Graph showing effect of route of administration on colistin Sputum concentrations](image)
Typical fit

CMS

Colistin

Plasma Conc. (mg/L)

Time (h)

iv

Aerosol
Colistin nebulization (as CMS or not) presents an obvious biopharmaceutical advantage over IV administration to reach high and sustained intrapulmonary (ELF) concentrations...

... let’s wait for clinical trials results
Acknowledgements

- Patrice Gobin
- Isabelle Lamarche
- Aline Gontijo
- Matthieu Boisson
- Dorothée Balayn
- Matthieu Jacobs
- Nicolas Grégoire
- Sandrine Marchand
- Olivier Mimoz

- Florent Perin-Dureau (Hopital Foch, Suresnes)
- Patrice Diot (CHU Tours)