Pharmacokinetics of colistin in critically ill patients with multidrug-resistant Gram-negative bacilli infection

Journal Club presentation

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Acknowledgement to
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Objectives:

- Elaborate the study
- Assess the strengths and weaknesses of the study
- The applicability of the study results

INTRODUCTION:

- Polymyxin E, Discovered in the late 1940s for the treatment of gram-negative infections
- **FDA Approved** was in1961
- Colistin is a re-emerging to treat multidrug-resistant infections (MDR) in critically ill patients
- Two commercially available product :
  - Colistemethate sodium (CMS)
  - Colistin base

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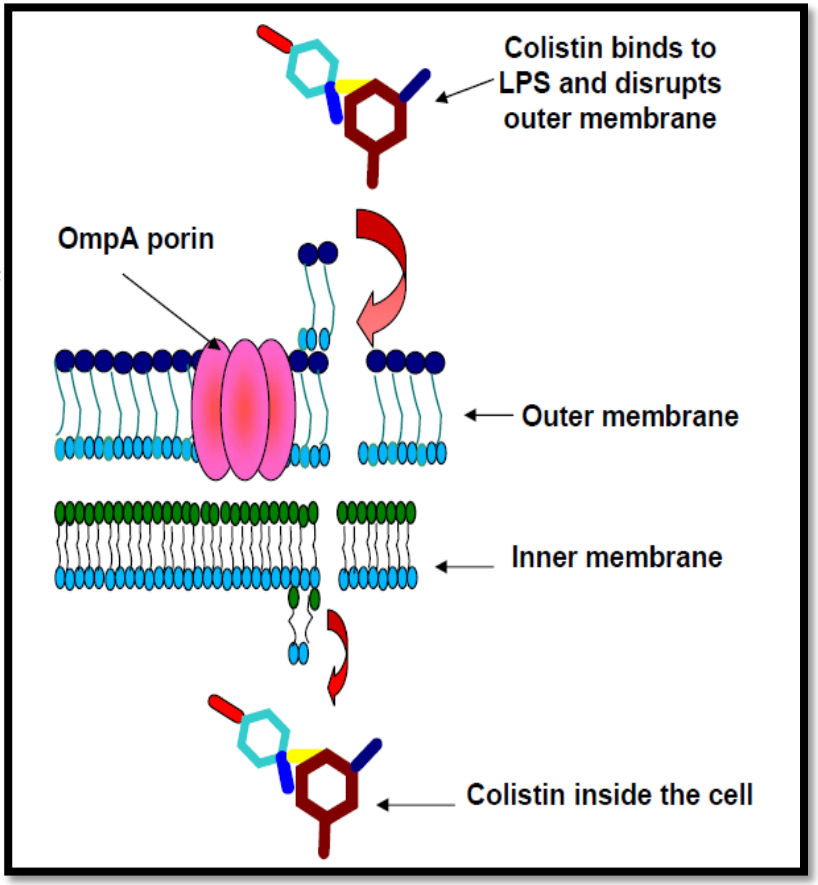
Mechanism of action

Bactericidal:

- Bind to lipopolysaccharides (LPS) & phospholipids in the outer cell membrane of G(-) bacteria
- Cause disruption of the outer cell membrane, leakage of intracellular contents, and bacterial death
- Neutralize LPS & prevent pathophysiologic effects of endotoxin



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Spectrum of activity

Susceptible microorganism	Resistant microorganism
•Pseudomonas & Acinitobacter baumannii. •E. coli, Enterobacter •H. influenza •Bordetella pertussis •Legionella, Klebsiella spp. •Salmonella spp., Shigella spp. •Mycobacterial spp.	•Proteus spp. •Providencia spp •Serratia spp. •Brucella spp

In addition, colistin is **NOT** active against **gram-positive aerobic cocci**, **gram-positive aerobic bacilli**, all **anaerobes**, **fungi**, and **parasites**.

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Pharmacokinetics of Colistemethate sodium (CMS)

- **Metabolism:**

  CMS $\xrightarrow{\text{Hydrolysis}}$ Colistin

  Not absorbed from GIT

- **Distribution :**

  Poor in (lung parenchyma, pleural cavity, pericardial fluids, and CSF)

  Time to peak: 10 min following IV administration

  Half-life elimination: 2-3 hours

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Pharmacokinetics of **Colistemethate sodium (CMS)**

- CMS is **tightly bound** to **membrane lipids** of **cells** in many body tissues, including liver, lungs, kidneys, brain, heart, and muscles
- Take **2-3 days** before the steady-state concentration was achieved

- **Execration**

Unchanged in urine (60%)

No biliary excretion

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Side effects

- **Nephrotoxicity (8-25%)**
  - Colistin induces tubular damage by increasing the epithelial cell membrane permeability, leading to leakage of contents and cell death.

- **Neurotoxicity (7%)**
  - Dizziness, weakness, facial and peripheral paresthesia, vertigo, visual disturbances, confusion and ataxia.

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PHARMACOKINETICS AND DISPOSITION

Pharmacokinetics of colistin in critically ill patients with multidrug-resistant Gram-negative bacilli infection

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Objective of the Study

To study the **single-dose** and **steady-state pharmacokinetics** of colistin in patients with multidrug-resistant **Gram-negative** bacilli infections

PICOT (Clinical Question)

P

- **Critically ill patients**
- Ventilator-associated pneumonia and bacteriologically documented MDR Gram-negative infections

I

- Colistimethate sodium

O

Safety outcomes the safety parameters:
- Mortality
- Adverse events
- Clinically significant changes in laboratory values.

PICOT (Clinical Question)

T

- **Duration** ranging from a minimum of **8** to a **maximum** of **14 days** depending on clinical need

PICOT OF THE STUDY (CONT'D)

- **Study Question:**
  - Is the pharmacokinetic of single-dose and steady state concentration of Colistimethate sodium in critically ill patients with GNB-(MDR)will be affected ?

Methodology

Study Design

- The design, prospective, non-comparative, open label study conducted between **September 2009 and August 2010**

METHODOLOGY

Excluded patients:

Diagnosed with

1. Myasthenia gravis
2. Pregnant and breastfeeding women

Inclusion & Exclusion Criteria patients

↓

Critically ill patients

(14 adults, 1 adolescent)

↓

Admitted to the medical intensive care unit (ICU) with bacteriologically documented

MDR Gram-negative infections

↓

Enrolled in the study after **written informed consent**

Defined as resistance to **three or more** of:

Penicillins

Cephalosporins,

Betalactams + Beta lactamase inhibitors,

Fluoroquinolones,

Carbapenems

Methodology

For each patient included:

- Detailed history
- Physical examination
- Health Evaluation II (**APACHE II**) scores
- Chest X-ray
- 12-lead electrocardiogram
- Blood and bronchoalveolar lavage specimens were obtained

Methodology

- Routine hematological
- Biochemical investigations were recorded at baseline.
- The baseline creatinine clearance(CLCR) (estimated by **Cockcroft–Gault formula**)
- **Women**: A urine pregnancy test was performed in child bearing age

METHODOLOGY:

- ***Drug administration:***
- Colistimethate sodium,

  administered **intravenously over 30 min** at a **dose calculated according** to the recommendations on the product's label

Patients	Dose
Weighing ≥**60 kg** normal renal function or with a CLCR **20 -50 ml/min**	2 million international units (MIU) Q8 h
CLCR of **10–20 ml/min**	2 MIU was Q12 h.
Patients weighing **<60 kg**	50,000 IU/kg/day in three divided doses at Q8h

Methodology

- ***Statistical analysis***

All significant associations were represented with the ***95 % confidence interval (CI)***

- ***Post hoc analysis:***
- Due to certain differences in the clinical outcomes between patients who had received the drug at different doses
- ***p value*** of <5 % was considered to be **significant**

Table 1 Demographic details

Patient number	Sex	Age (years)	Body weight (kg)	Dose (MIU) per day	Diagnosis	CL_{CR} (ml/min)	APACHE II scoring	Outcome	Specimen	Bacteriological profile
1.	M	22	60	6	Guillain-Barre syndrome	49.16	13	Survived	Bronchoalveolar lavage	*Acinetobacter baumanii*
2.	F	30	65	6	Polymyositis	167.28	6	Survived	Bronchoalveolar lavage	*Acinetobacter baumanii* and *Pseudomonas spp.*
3.	F	15	50	2.5	Viral encephalitis	81.94	5	Survived	Bronchoalveolar lavage	*Acinetobacter baumanii* and *Pseudomonas spp.*
4.	M	22	65	6	Guillain-Barre syndrome	133.8	5	Survived	Bronchoalveolar lavage	*Acinetobacter baumanii* and *Pseudomonas spp.*
5.	F	27	50	2.5	Acute respiratory distress syndrome/ Pulmonary tuberculosis	84	16	Died	Blood	*Klebsiella pneumoniae* and *Pseudomonas spp.*
6.	F	21	55	2.75	Organophosphorus poisoning	99.89	11	Died	Bronchoalveolar lavage	*Acinetobacter spp.*
7.	F	37	55	2.75	Organophosphorus poisoning	70.39	9	Died	Bronchoalveolar lavage	*Pseudomonas spp.*
8.	M	35	60	6	Acute respiratory distress syndrome	105.4	6	Survived	Bronchoalveolar lavage	*Acinetobacter spp.*
9.	M	20	62	6	Tetanus	172.22	10	Survived	Blood	*Pseudomonas aeroginosa*
10.	M	19	62	6	Guillain-Barre syndrome	173.65	4	Survived	Bronchoalveolar lavage	*Acinetobacter baumanii* and *Pseudomonas spp.*
11.	M	37	68	6	Nephrotic syndrome	154.4	14	Died after completion	Bronchoalveolar lavage	*Acinetobacter spp.*
12.	F	27	60	6	Frontal arteriovenous malformation	125	11	Survived	Bronchoalveolar lavage	*Acinetobacter spp.*
13.	M	40	60	6	Guillain-Barre syndrome	88.65	6	Survived	Bronchoalveolar lavage	*Acinetobacter spp.*
14.	F	22	65	6	Guillain-Barre syndrome	220.8	8	Survived	Bronchoalveolar lavage	*Acinetobacter spp.* and *Methicillin Resistant Staphylococcus aureus*
15.	M	35	85	6	Cerebrovenous accident	126.48	14	Died	Bronchoalveolar lavage	*Acinetobacter spp.*

Table 2 Bacteriological, clinical and safety outcomes

Patient number	Bacteriological outcome	Clinical outcome	
1.	Growth persisted but sensitive to colistin	Clinical improvement	[illegible]zymes
2.	Growth persisted but sensitive to colistin	Clinical cure	Elev[illegible]
3.	Growth persisted but sensitive to colistin	Clinical improvement	[illegible]a, convulsion
4.	Eradication of pathogen	Clinical cure	
5.	Bacteriological response could not be performed	Clinical failure	
6.	Bacteriological response could not be performed	Clinical failure	Dea[illegible]
7.	Bacteriological response could not be performed	Clinical failure	Elevated liver enzymes, death
8.	Eradication of pathogens	Clinical cure	None
9.	Growth persisted but sensitive to colistin	Clinical improvement	Leg pain
10.	Eradication of pathogens	Clinical cure	None
11.	Eradication of pathogens	Clinical cure	None
12.	Growth persisted but sensitive to colistin	Clinical improvement	Death
13.	Growth persisted but sensitive to colistin	Clinical cure	None
14.	Bacteriological response could not be performed	Clinical failure	Death
15.	Growth persisted but sensitive to colistin	Clinical improvement	None

possibly related

possible causal relation to the drug

RESULTS:

Table 3 Summary of the single-dose and steady-state pharmacokinetic data

Pharmacokinetic parameter	Single-dose PK value[a]	Steady-state PK value[a]
C_{max} (μg/ml)	4.6 (2.5–23.2)	5.4 (1.8–21.8)
AUC_8 (mg.hr/l)	11.2 (5.4–16.4)	15.7 (5.0–26.7)
AUC_∞ (mg.hr/l)	12.9 (5.6–18.9)	19.7 (5.2–41.8)
$t_{1/2}$ (h)	2.7 (1.1–4.6)	3.3 (1.2–5.4)
V_d (l/kg)	0.3 (0.2–0.5)	0.3 (0.2–0.5)
CL (ml/min/kg)	1.3 (1.0–2.1)	1.1 (0.7–1.9)
C_{max}/MIC (*Acinetobacter* spp.)	13.4 (1.3–40.3)	26.3 (0.9–64.9)
C_{max}/MIC (*Pseudomonas* spp.)	3.2 (1.6–23.1)	3.8 (2.3–10.9)

Result:

- The four patients who weighed≤60 kg received a considerably **smaller** dose of colistimethate sodium (2.5 M IU/day and 2.75 M IU/day)

- In contrast, 9 of the 11 who weighed>60 kg and received 6 MIU/day survived, indicating that **adequate dosing** is necessary for best results

Author's Conclusion

- Among the patients enrolled in our study, colistin was well tolerated, and no events of either renal toxicity or neurotoxicity were noted at the dose administered.

- Cmax was found to be comparable to that of previous studies but appears to be inadequate to maintain the Cmax/MIC ratio to an optimal level—at least for Pseudomonas spp.

Author's Conclusion

- Dose revision may need to be considered for patients weighing≤60 kg
- Overall, the pharmacokinetic–pharmacodynamic information obtained from this study may be a useful tool in antibiotic selection and implies therapeutic benefits of colistin in hospital-acquired MDR Gram-negative bacilli infections

Strengths and Weaknesses

- **Strengths**
  - Prospective study design
  - First trial in India
  - Provide a pharmacokinetic data for critical ill patients
  - It was assessing two different doses of colistmethate sodium
  - Use of post hoc analysis

Strengths and Weaknesses (Cont'd)

- **Weaknesses**
  - Open labeled, and non comparator
  - Bias can't be excluded

Recommendation

- Colistin is a re-emerging to treat multidrug-resistant infections in critically ill patients.
- Time-averaged exposure to colistin is a more important target in the clinical practice than the achievement of high colistin peak concentrations

Recommendation

- New recommended dose of colistin in sever infections is more effective without significant renal toxicity

- Recommended dose : ≤60 kg bodyweight: **50 000 IU– 75 000 IU/kg per day in three divided doses, equivalent to 4–6 mg/kg per day colistimethate sodium**

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Recommendation

- >60 kg bodyweight:
  1–2 million IU three times a day, equivalent to 80–160 mg colistimethate sodium three times per day

- Product-recommended upper limit dose for a 60 kg patient **480 mg of colistimethate sodium per day** for patient with **normal renal function**

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Thank you

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