Meropenem 1g q8h by 3hrs-extended infusion improves effectiveness in critically ill burn patients at the earlier period of septic shock against P. aeruginosa intermediate susceptibility 4-8mg/L

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Introduction:

Meropenem is largely prescribed to critically ill septic patients with nosocomial infections caused by Gram-negative strains. Recommended dose cannot achieve the target, once serum levels result below those required for effectiveness MIC > 2mg/L, pathogens.

Objective:

Rational of study was to investigate drug effectiveness after the 3hrs-extended infusion by application of pharmacokinetics-pharmacodynamics (PK/PD).
Approach in septic burn patients to avoid P. aeruginosa resistance.
Develop and validate a bioanalytical LC-MS/MS assay

Methods:

Ethical Comitee approval:CAAE nº 07525118.3.0000.0068

Characteristics of patients admission in ICU	
Medians (IQR)	**Proportion n=12 patients**
31 (24-35) yrs	6/6 Gender (M/F)
72(61-75) kg	8/12 Inhalation injury
32(19-43) %TBSA	9/12 Mechanical ventilation
SAPS3 59 (44-60)	12/12 vassopressors requirement

3-hrs Extended Infusion Strategy - Critically ill Septic Burn Patients with vasopressors
Meropenem n =12
Regimen: 1.0g q8h (12 patients)
Blood (2mL) was sampling at the steady state level: 3rd_5th hr of start infusion
TDM: new bioanalytical method LC MS/MS for simultaneous serum monitoring in ICU patients of our hospital
PK: Noncompartmental data analysis: $t(1/2)\beta$: half-life, CL_T: clearance, Vd^{ss} : vol. distribution
PK/PD approach: predictive index of effectiveness (%fDT>MIC). Target considered: 100%fDT>MIC (MIC>2mg/L)

SAMPLE PREPARATION

100µL serum
+
10µL of 20µg/mL Mix internal standard (IS) : Meropenem D6 and piperacillin D5
+
500µL of acetonitrile LCMS grade
↓
Vortexed (10 seconds)
↓
Centrifuged 13500 rpm (1440g)for 8 minutes
↓
1:1 Supernatant dilution with SRW H_20
↓
Injected 10µL into Waters® Acquity TQD UPLCMS/MS

Analytical column

Hypersil Accucore C18 100 × 2.1 mmx2.6 µm

Mobile phase at 0.4 mL/min (gradient elution) :
[A] : $HCOONH_4$ 2 mM + 0.1% HCOOH (water)
[B]: Acetonitrile + 0.1% HCOOH

Mass Spectrometer Settings

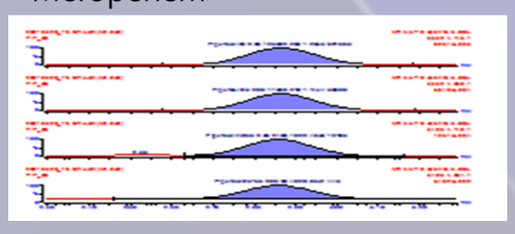
MRM Positive mode
ESI voltage: 2.95kV
Cone Voltage: 36V
Dessolvation temperature: 200°C
MRM Transition Settings
Meropenem : 384.1> 141.1 (quantification); 384.1> 254.1 (confirmation)
Internal standard Meropenem D6 : 390.1> 147.1 (quantification); 390.1 > 260.1 (confirmation)

Results:

Bioanalytical Method LC-MS/MS

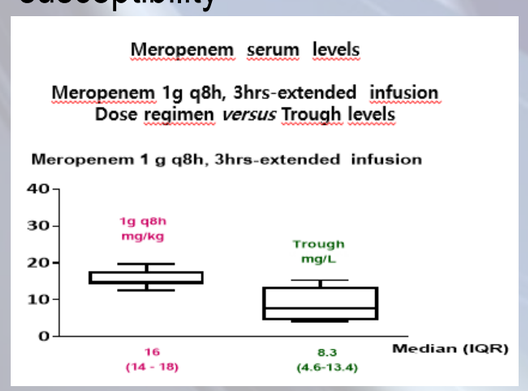
1. It was developed and validated a liquid chromatographic tandem mass spectrometry method to quantify Meropenem-Piperacillin in serum simultaneously
2. A high specific and selective bioanalytical method was developed and validated in the Central Laboratory of our hospital
3. Good linearity 1-250 mg/L (r^2: 0.995), sensitivity 1mg/L precision and accuracy
4. LC-MS/MS is considered the gold standard for TDM_antimicrobials.

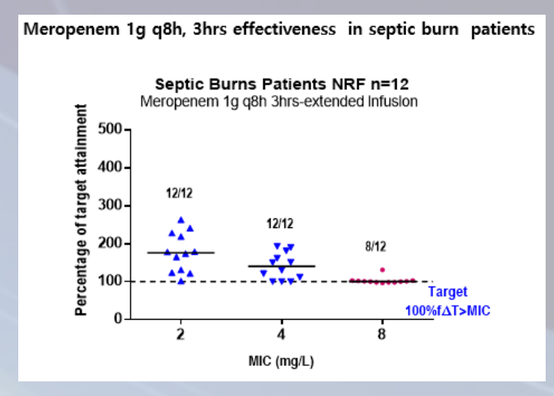
Serum sample chromatogram of patient with 20.1 µg/mL of Meropenem

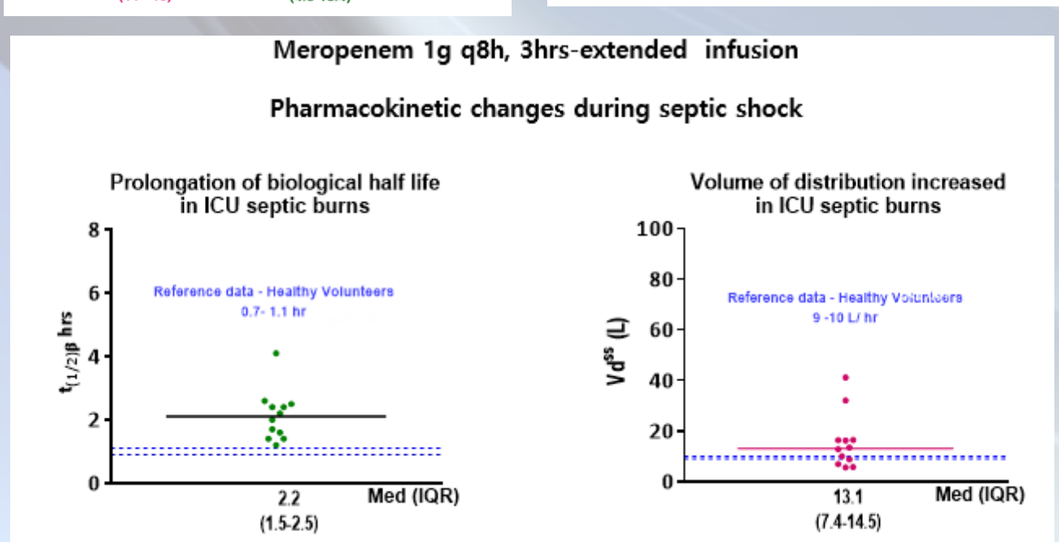


Desired outcome reached
Clinical and microbiological cure against Gram negative (*P. aeruginosa*) nosocomial pathogens

Meropenem: clinical and microbiological cure occurred occurred for all patients by eradication of pathogens after the extended infusion of meropenem up to MIC 4 mg/L and extended to MIC 8mg/L in 50% of patients *P. aeruginosa* isolates of intermediate susceptibility







•Conclusion:

•Considering the first septic shock in ICU of burn patients, the superiority of the 3hrs-extended infusion was demonstrated after 1g q8h of meropenem administered by 3 hrs-extended infusion.and must be applied to critically ill septic patients to reach soon the desired outcome based on PK/PD approach.
•LC-MS/MS is a gold standard bioanalytical method in Clinical laboratories and has been developed and validated for monitoring Meropenem in Human Serum.
•Then, this strategy is considered an important tool to assess drug effectiveness, mainly at the earlier period of septic shock.

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