

Pharmacokinetics-pharmacodynamics approach for comparison of Piperacillin/Tazobactam effectiveness, two dose regimens in septic burn patients.

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Introduction:

Piperacillin/tazobactam is 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 by application of pharmacokinetics-pharmacodynamics (PK/PD).

Approach in septic burn, with vasopressors, patients mainly against intermediate susceptibility pathogens.

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=16 patients	
32 (24-41) yrs	12/4	Gender (M/F)
70(62-75) kg	13/16	Inhalation injury
22(14-37) %TBSA	16/16	Mechanical ventilation
SAPS3 62 (35-67)	16/16	vassopressors requirements

3-hrs Extended Infusion Strategy - Critically ill Septic Burn Patients with vasopressors

Piperacillin-Tazobactam n =16

Regimen: 4.5g q8h (5 patients) or q6h (11 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) β : 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

100 μ L serum
+
10 μ L of 20 μ g/mL Mix internal standard (IS) :
Meropenem D6 and piperacillin D5
+
500 μ L of acetonitrile LCMS grade
↓
Vortexed (10 seconds)
↓
Centrifuged 13500 rpm (1440g) for 8 minutes
↓
1:1 Supernatant dilution with SRW H₂O
↓
Injected 10 μ L into Waters® Acquity TQD
UPLCMS/MS

Analytical column

Hypersil Accucore C18 100 x 2.1 mm x 2.6 μ m

Mobile phase at 0.4 mL/min (gradient elution) :

[A] : HCOONH₄ 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

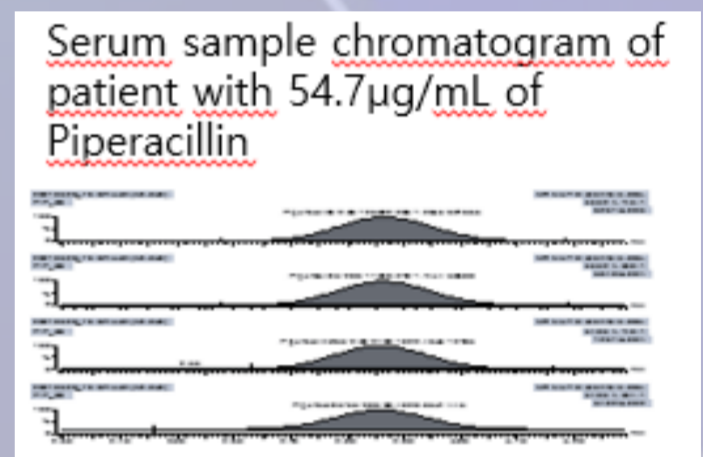
Piperacillin : 535.2> 143.1 (quantification); 535.2> 359.1 (confirmation)

Piperacillin D5 : 540.3> 148.1 (quantification); 540.3 > 364.1 (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.

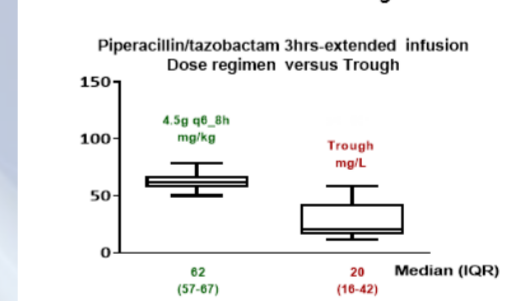


Desired outcome reached

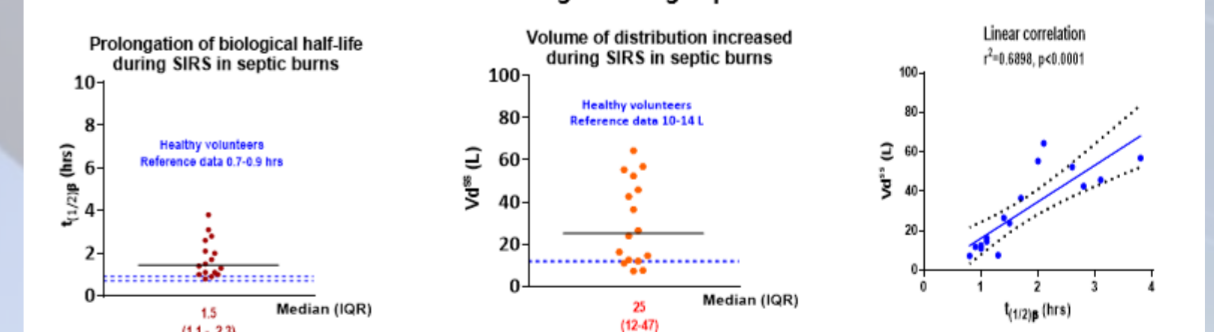
Clinical and microbiological cure against Gram negative (*k.pneumoniae* and *P. aeruginosa*) nosocomial pathogens

Piperacillin: clinical and microbiological cure occurred in 11 patients (18 g/day) by Tazocin 4.5g q6h 11. Dose adjustment was required in 5/16 for effectiveness achievement in the rest of them (5 patients receiving initial therapy 4.5g every 8 hrs) up to MIC 16 mg/L strains.

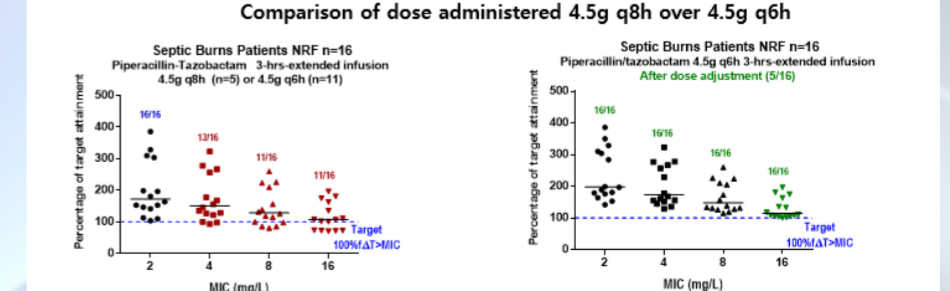
TAZOCIN 4.5g q8h_q6h, 3hrs extended infusion Dose administered versus Trough levels



TAZOCIN 4.5g q6-8h, 3hrs-extended infusion Pharmacokinetic changes during septic shock



PTZ 3hrs extended infusion Comparison of dose administered 4.5g q8h over 4.5g q6h



Conclusion:

- Considering the first septic shock in ICU of burn patients, the superiority of the 3hrs-extended infusion was demonstrated after piperacillin-tazobactam 4.5g q6h over 4.5g q8h. Consequently, after dose adjustment clinical cure was reached for all patients.
- Piperacillin serum monitoring must be done in critically ill septic patients to reach soon the desired outcome based on PK/PD approach.
- Then, this strategy is considered an important tool to assess drug effectiveness, mainly at the earlier period of septic shock.