Pharmacokinetics of piperacillin-tazobactam in critically-ill patients receiving extracorporeal membrane oxygenation (ECMO)

Vesa Cheng[1,2], Kiran Shekar[2], Mohd H. Abdul-Aziz[1], Hergen Buscher[3], Amanda Corley[2], Eileen Gilder[4], Paul Jarrett[2], India Lye[2], Shay McGuinness[4], Rachael Parke[4], Vin Pellegrino[5], Steven C. Wallis[1], Susan Welch[3], John F. Fraser[2], Jason A. Roberts[1] on behalf of ASAP ECMO investigators.
[1]Faculty of Medicine, The University of Queensland, Brisbane, Australia. [2]Critical Care Research Group, Adult Intensive Care Services, The Prince Charles Hospital, Brisbane, Australia. [3]Intensive Care Services, St Vincent's Hospital, Sydney, Australia. [4]Cardiothoracic and Vascular Intensive Care Unit, Auckland City Hospital, Auckland, New Zealand. [5]Intensive Care Services, The Alfred Hospital, Melbourne, Australia.

INTRODUCTION:

- ECMO is increasingly being used in the adult population with severe cardiorespiratory failure
- Minimal information exists on the optimal antimicrobial dosing in this population
- Aim: To describe the pharmacokinetics (PK) of piperacillin in critically ill patients who are receiving ECMO in the ICU.

METHOD:

- Prospective multi-centre, open-label PK study
- Critically ill adults from five ICU's in Australia and New Zealand were eligible for inclusion
- Serial blood sampling was taken over one-dosing interval with samples measured by a validated high-performance liquid chromatography with ultraviolet detection (HPLC-UV) assay
- PK parameters were estimated via a non-compartmental approach.

RESULTS:

Seven critically ill patients were recruited in the study, summarised in Table 1:

Table 1: Patient demographic and clinical characteristics[a] (n = 7)	
Age in years	58.0 (53.0 – 67.0)
Male, n (%)	5 (71.4)
Weight (kg)	90.0 (75.0 – 112.0)
BMI (kg/m^2)	27.8 (23.1 – 36.7)
APACHE II	23.5 (15.3 – 36.3)
SOFA	7.5 (5.3 – 9.8)
ECMO modality, n (%)	
Veno-arterial (VA)	4 (57.1)
Veno-venous (VV)	3 (42.9)
ECMO duration (days)	5.0 (1.0 – 8.0)
Serum creatinine concentration (μmol/L)	71.0 (46.0 – 122.0)
Creatinine clearance (mL/min)	97.6 (67.3 – 116.5)
Blood urea nitrogen (mmol/L)	14.4 (10.5 – 18.6)
Albumin (g/L)	29.0 (28.0 – 40.0)

BMI, body mass index; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; ECMO, extracorporeal membrane oxygenation
[a]Data are presented as median (IQR) or number (percentage).

Figure 1: Mean +/- standard deviation of piperacillin plasma concentration over time

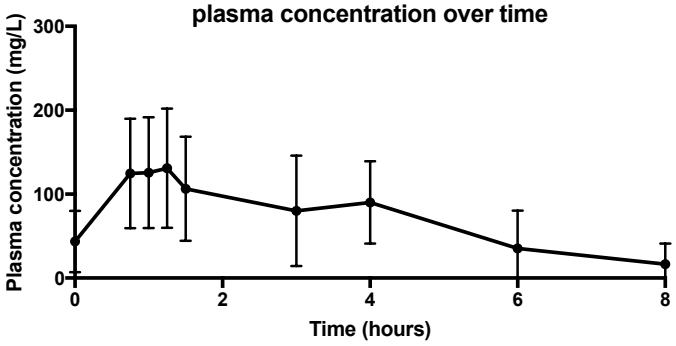

Table 2: PK parameters estimates

Table 2: Pharmacokinetic parameter estimates[a] (n = 7)	
AUC_{0-t} (mg/L·h)	310.96 (162.41 – 769.09)
AUC_{0-inf} (mg/L·h)	313.52 (178.80 – 1220.96)
$AUMC_{0-t}$ (mg/L·h)	611.18 (273.12 – 2488.16)
$AUMC_{0-inf}$ (mg/L·h)	699.54 (421.77 – 10622.22)
C_{max} (mg/L)	164.09 (94.36 – 222.99)
K_e (h^{-1})	0.33 (0.10 – 0.41)
$t_{1/2}$ (h)	2.13 (1.68 – 6.93)
CL (L/h)	12.76 (3.28 – 22.37)
CL/kg (L/h/kg)	0.12 (0.06 – 0.20)
V_d (L)	32.76 (22.82 – 68.70)
V_d/kg (L/kg)	0.29 (0.28 – 0.61)

AUC_{0-t}, area under a curve from time 0 to time t; AUC_{0-inf}, area under a curve from time 0 to infinity; $AUMC_{0-t}$, area under a moment curve from time 0 to time t; $AUMC_{0-inf}$, area under a moment curve from time 0 to infinity; C_{max}, maximal concentration; K_e, elimination rate constant; $t_{1/2}$, half-life; CL, clearance; V_d, volume of distribution.
[a]Data are presented as median (IQR) or number (percentage).

- Up to 4-fold variations were observed in these parameter estimates
- PK estimates are generally consistent with published studies in critically ill patients who are receiving ECMO.

CONCLUSION:

- Heterogeneity of results demonstrates significant PK variability in piperacillin
- Further analysis with compartmental modelling to develop robust dosing guidelines to optimise pharmacotherapy in these patients is required.