Population Pharmacokinetics of Imipenem on Burn Patients

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Physiopathology of Burns

Fig. 2. Mechanisms underlying augmented renal clearance (ARC) in the critically ill. CO = cardiac output; GFR = glomerular filtration rate; IV = intravenous; RBF = renal blood flow; SIRS = systemic inflammatory response syndrome; ▲ indicates increase.

Udy et. al., Clin. Pharmacokinetics (2010)
Imipenem for infection on burn patients

- Carbapenems was most consumed antibiotics
- Imipenem was first choice among carbapenems for severe infection in burn patients.
- The resistance of hospital infectious pathogens was emerging [2]

1. AHFS Drug information (2011), imipenem-clilastatin
2. Luong QA (2016), Journal of disaster medicine and burns injuries [Vietnamese]
Pharmacokinetic variabilities on burned patients

Inter Individual variation (IIV)

Occasion 1

Baseline

Patient 1

Patient 2

Renal failure

Patient n

Occasion 2

ARC

AKI

Inter occasion variation (IOV)

Should empirical dose fit all?
Pharmacokinetic of imipenem on burned patients

The study aimed:

- To estimate population PK parameters (including IIV and IOV)

- To explore potential covariates influencing PK properties of imipenem on burn patients.
Methods – Patients and data collection

Burned patients in Intensive Care Unit, National Institute of Burns of Vietnam;

**Inclusion**
- Age ≥ 18
- Hospitalized within 72 hours after injury
- Injury ≥ 20% body surface area
- Imipenem indication

**Exclusion**
- Renal failure or other serious conditions before injury.
- Refuse to participate into the study

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**Day 1**
- Collect Baseline information

**From day 2**
- Inclusion/exclusion criteria
- Imipenem indication; Informed consent obtained
- Hemodialysis, transferred, death,...

**Daily data collection:**
- Clinical, laboratory test, treatments, renal function, pharmacokinetic sampling.
Methods - Pharmacokinetic sampling

Sampling occasions:
+ At steady state (After 12 h)
+ 5-7 days after hospitalization
+ Optional: AKI (AKIN 2 or higher)

Sample set of one occasion:
+ 2 plasma samples (HPLC analysis)
+ A 8h urine sample
+ A plasma creatinine sample
  \[ (ARC: \text{8h-urine Clcr} > 130 \text{ ml/min/1,73m}^2) \]

Data analysis
+ Nonlinear mixed effect model
+ Monolix 2016R1
## Results – Baseline and follow up monitoring

<table>
<thead>
<tr>
<th>Parameters</th>
<th>n (%)</th>
<th>Parameters</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (Male)</td>
<td>15 (62.5)</td>
<td>Imipenem dosage (n=47)</td>
<td></td>
</tr>
<tr>
<td>Age (years) (#)</td>
<td>38.9 (17.5)</td>
<td>1g q.i.d.</td>
<td>38 (80.9)</td>
</tr>
<tr>
<td>SOFA score ($)</td>
<td>5 (4 - 6)</td>
<td>1g t.i.d.</td>
<td>7 (14.9)</td>
</tr>
<tr>
<td>APACHE II score ($)</td>
<td>14 (11 – 18)</td>
<td>0,5g q.i.d.</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>eGFR (ml/min/1,73m²)</td>
<td>85.9 (29.4)</td>
<td>0,5g t.i.d.</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>Burned surface (m²) (#)</td>
<td>50.8 (17.3)</td>
<td>Imipenem courses (days) (#)</td>
<td>7.5 (6 – 10)</td>
</tr>
<tr>
<td>To hospitalization (hrs) ($)</td>
<td>4.5 (3 - 9.5)</td>
<td>Patients with ARC (N=24)</td>
<td>13 (54.2)</td>
</tr>
<tr>
<td>To imipenem use (days)($)</td>
<td>5 (3-7)</td>
<td>Occations with ARC (N = 47)</td>
<td>18 (38.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Occation(s) per patient</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4</td>
<td>8</td>
</tr>
</tbody>
</table>

($)$ mean (interquartile range);
(#) mean (standard deviation)
**Results – Basic pharmacokinetic model**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimation (95% CI)</th>
<th>IIV (CV%)</th>
<th>IOV (CV%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pop. Vd (L)</td>
<td>33.5 (28.2-38.8)</td>
<td>18.2</td>
<td>15.6</td>
</tr>
<tr>
<td>IIV (CV%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IOV (CV%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residual (CV%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**From Pop PK modelling:** one compartment with proportional error showed best fit.
## Results – Covariate model

<table>
<thead>
<tr>
<th></th>
<th>Estimation (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vd (L)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-ARC</td>
<td>32.6 (26.7-38.5)</td>
<td>0.83</td>
</tr>
<tr>
<td>ARC</td>
<td>33.6 (26.5-40.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Age (10 years) (*)</strong></td>
<td>0.874 (0.802-0.952)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Cl (L/h)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-ARC</td>
<td>16.4 (14.24-18.56)</td>
<td></td>
</tr>
<tr>
<td>ARC</td>
<td>24.9 (20.6-29.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Age (10 years) (*)</strong></td>
<td>0.872 (0.816-0.932)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

- 10 years older, ↓ 13% Vd
- 10 years older, ↓ 13% Cl

*Age was centralized by mean value of 38.9; (*): present relative reduction of parameters;*

Elimination rate may be unchanged. Dose adjustment is not necessary.
Inter-occasions variability, The risk?

Simulated imipenem concentration in a burn patient (one compt.)

Fixed: Dose **1000mg** IV infusion for **2 h**; dose interval **6h**; Vd **33 L**

**Cl**: 15 (L/h)  
**Cl**: 25 (L/h)  
**Cl**: 7.5 (L/h)

**Target fT>MIC NOT achieved?**  
**Toxicity?**  
**MIC = 4mg/L**
Conclusions

• Imipenem PK parameters (Cl, Vd) substantial varied between burned patients and between occasions.

• Age was significant covariate predicting Cl and Vd, ARC showed no effect on Vd but it did predict Cl.

• Target PK/PD may not be attained in ARC patients. Monitoring urine Clcr may be the solution for detecting ARC and then adjusting imipenem’s dose to ensure the efficacy.