Influence of Real-Time Therapeutic Drug Monitoring on Carbapenems prescription amongst severely Burn Patients

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Services of:
1. Pharmacy
2. Intensive Care Medicine
3. Biomedicine
4. Infectious Diseases
1. Introduction

**Infectious risk** $\uparrow$
- Loss of dermal barrier
- Avascularity of the wound tissue
- Immune deficits
- Repeated surgeries, …

**Carbapenems**
- Beta-lactam ring
- Broad-spectrum antibiotics
- Stability against hydrolysis (most $\beta$-lactamases)
- « Time-dependent » bactericidal effect
- PD parameter of efficacy: $T > \text{MIC}$

**Modifications of drugs PKs**
- Patient (age, $\text{Cl}_{\text{creat}}$, burn, sepsis, …)
- Time from burn (acute phase / hypermetabolic state)

**TDM**
- Plasma concentration measurement
- Dosage individualization
- $\uparrow$ therapeutic efficacy, $\downarrow$ toxicity
- Candidate drugs? Long term therapy, significant inter-patient PK variability, low intra-patient PK variability, consistent concentration-efficacy/toxicity relationships, …
2. Method

Study period: 2001-2011
✓ Period 1: 2001- June 2007
✓ Period 2: June 2007 - 2011

Carbapenems
✓ Imipenem/cilastin
✓ Meropenem

Carbapenems

- Period 1: 2001- June 2007
  - Imipenem/cilastin
  - Meropenem a) June 2007: 1 day / week
  - b) January 2010: 4 days / week

Carbapenems

« Real-Time » TDM

1. Number of doses
2. Cumulative doses [grams]
3. Number of treatment days
4. Number of cures

Number of TDM requests
3. Results

a) Study flow chart

366 burn patients

230 patients receiving antibiotics

136 patients not receiving antibiotics

110 carbapenems

120 other antibiotics

48 imipenem/cilastin only

39 meropenem only

23 both imipenem/cilastin and meropenem
### b) Burn population with carbapenems (n = 110)

<table>
<thead>
<tr>
<th></th>
<th>2001 - 2011</th>
<th>Period 1 TDM on request</th>
<th>Period 2 Real-time TDM</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 110)</td>
<td>(n = 63)</td>
<td>(n = 47)</td>
<td></td>
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<tr>
<td><strong>Demographics</strong></td>
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<tr>
<td>Age, yrs (median [p25;p75])</td>
<td>45.50 [29.00;59.00]</td>
<td>42.00 [28.00;58.00]</td>
<td>50.00 [34.00;61.00]</td>
<td>0.18</td>
</tr>
<tr>
<td>Male (n, %)</td>
<td>62 (56.4)</td>
<td>37 (58.7)</td>
<td>25 (53.2)</td>
<td>0.70</td>
</tr>
<tr>
<td><strong>Burn characteristics</strong></td>
<td></td>
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<tr>
<td>TBSA (median [p25;p75])</td>
<td>30.00 [19.75;46.25]</td>
<td>30.00 [20.00;45.00]</td>
<td>28.00 [17.00;50.00]</td>
<td>0.92</td>
</tr>
<tr>
<td>&lt; 20% (n, %)</td>
<td>27 (24.5)</td>
<td>13 (20.6)</td>
<td>14 (29.8)</td>
<td>0.37</td>
</tr>
<tr>
<td>20-40% (n, %)</td>
<td>48 (43.6)</td>
<td>32 (50.8)</td>
<td>16 (34.0)</td>
<td>0.08</td>
</tr>
<tr>
<td>41-60% (n, %)</td>
<td>23 (20.9)</td>
<td>13 (20.6)</td>
<td>10 (21.3)</td>
<td>1.00</td>
</tr>
<tr>
<td>&gt; 60%</td>
<td>12 (10.9)</td>
<td>5 (7.9)</td>
<td>7 (14.9)</td>
<td>0.35</td>
</tr>
<tr>
<td>Inhalation (n, %)</td>
<td>56 (50.9)</td>
<td>35 (62.5)</td>
<td>21 (37.5)</td>
<td>0.33</td>
</tr>
<tr>
<td>Ryan Score (mean ± SD)</td>
<td>1.06 ± 0.67</td>
<td>1.06 ± 0.64</td>
<td>1.06 ± 0.70</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Length of stay (median [p25;p75])</td>
<td>32.00 [18.75;53.25]</td>
<td>31.00 [18.00;51.00]</td>
<td>33.00 [20.00;66.00]</td>
<td>0.47</td>
</tr>
<tr>
<td>Burn ICU mortality (n, %)</td>
<td>12 (10.9)</td>
<td>5 (7.9)</td>
<td>7 (14.9)</td>
<td>0.35</td>
</tr>
</tbody>
</table>
c) The evolution of the prescription

Figure 1: The use of Imipenem/cilastin (diamond dash line) and Meropenem (square full line) from 2001 to June 2007 (period 1) and July 2007 to 2011 (grey, period 2) expressed as the total amount of antibiotic used each year with the total number of patients admitted to the Burn ICU during the corresponding year.

Figure 2: Daily doses of Imipenem/cilastin (dashed-line) and Meropenem (full-line) over period 1 (2001 - June 2007) and period 2 (July 2007 - 2011).
<table>
<thead>
<tr>
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<th>Period 2</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>TDM on request</td>
<td>Real-time TDM</td>
<td></td>
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<tr>
<td><strong>Imipenem</strong></td>
<td>(n = 53)</td>
<td>(n = 18)</td>
<td></td>
</tr>
<tr>
<td>Course per year (mean ± SD)</td>
<td>10.29 ± 5.50</td>
<td>4.20 ± 2.28</td>
<td>0.04</td>
</tr>
<tr>
<td>Daily dose (grams) (median [p25;p75])</td>
<td>1.60 [1.23; 1.77]</td>
<td>1.81 [1.54; 2.44]</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Meropenem</strong></td>
<td>(n = 24)</td>
<td>(n = 38)</td>
<td></td>
</tr>
<tr>
<td>Course per year (mean ± SD)</td>
<td>4.43 ± 2.57</td>
<td>10.80 ± 5.72</td>
<td>0.02</td>
</tr>
<tr>
<td>Daily dose (grams) (median [p25;p75])</td>
<td>2.29 [2.00; 3.92]</td>
<td>2.61 [2.00; 3.95]</td>
<td>0.77</td>
</tr>
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</table>
Figure 3: Correlation between the number of TDM requests and the daily dosage of imipenem / cilastin
4. Conclusion

Real-time availability of TDM $\rightarrow$ significative changes in carbapenems prescription.

Consumption
- **Imipenem/cilastin**: ↓ from 10.3 cures/year (period 1) $\rightarrow$ 4.2 cures/year (period 2)
- **Meropenem**: ↑ from 4.4 cures/year (period 1) $\rightarrow$ 10.8 cures/year (period 2)

Daily doses
- **Imipenem/cilastin**: ↑ from 1.6g (period 1) $\rightarrow$ 1.8g (period 2)
- **Meropenem**: peak of 5.0g. (2006) $\rightarrow$ 2.7g (2011)

Clinicians were justified in:
- Maintaining meropenem dosage
- Increasing the dosage of imipenem/cilastin

Further prospective studies are required to determine if these changes will impact treatment efficacy and safety.