Exposure to intravenous posaconazole in a critically ill patient during extracorporeal membrane oxygenation (ECMO): first case report

Ruth Van Daele, PharmD
Joost Wauters, MD, PhD
Roger Brüggemann, PharmD, PhD
Frédéric Cotton, PharmD, PhD
Isabel Spriet, PharmD, PhD
1. Background
2. Methods
3. Results
4. Discussion
1. Background

IV formulation posaconazole

- Bioavailability 100%
- Administration in mechanically ventilated patients

But...

- PK data in critically ill and ECMO are scarce
Question 1

Do you think ECMO can have an influence on the plasma posaconazole concentration?

1. Yes

2. No
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1. Yes
2. No
1. Background

ECMO can possibly influence drug levels

- Vd ↑
- Sequestration circuit
1. Background

ECMO can possibly influence drug levels

- Vd ↑

- Sequestration circuit

GOAL: posaconazole exposure in critically ill with ECMO

Posaconazole = lipophilic molecule

GOAL: posaconazole exposure in critically ill with ECMO
## 2. Methods

### Study drug

<table>
<thead>
<tr>
<th>Indication</th>
<th>posaconazole prophylaxis for prevention of influenza associated aspergillosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>Day 1                        300mg BD</td>
</tr>
<tr>
<td></td>
<td>Day 2-7                      300mg OD</td>
</tr>
</tbody>
</table>

### Plasma sampling

- Early & late day
- Before and 1.5, 4, 8, 12 and 24h after start infusion
# 3. Results

<table>
<thead>
<tr>
<th>Population</th>
<th>Time</th>
<th>$C_{\text{min}}$ (mg/L)</th>
<th>$C_{\text{avg}}$ (mg/L)</th>
<th>$C_{\text{max}}$ (mg/L)</th>
<th>AUC$_{0-24}$ (mg.h/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU+ECMO</td>
<td>Day 2</td>
<td>Day 2: 0.77</td>
<td>1.32</td>
<td>3.64</td>
<td>31.74</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Day 3: 0.96</td>
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<td></td>
<td></td>
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<tr>
<td></td>
<td>Day 7</td>
<td>Day 7: 1.00</td>
<td>1.19</td>
<td>1.91</td>
<td>28.52</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Day 8: 0.79</td>
<td></td>
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![Graph showing drug concentration over time](image)
4. Discussion

All $C_{\text{min}} > 0.7$ mg/L but < 1.25 mg/L

Day 2: 0.77
Day 3: 0.96
Day 7: 1.00
Day 8: 0.79

4. Discussion

within EMA target range of 0.5 – 2.5 mg/L

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The exposure target range for the use of POS IV solution in subjects was set as below:

Mean steady-state $C_{avg}$ of around 1,200 ng/mL (or AUC[0-24] of 28,800 ng.hr/mL) with at least 90% of the subjects between 500 ng/mL (or AUC[0-24] of 12,000 ng.hr/mL) and 2,500 ng/mL (or AUC[0-24] of 60,000 ng.hr/mL); and

- No subject with mean $C_{avg}$ at steady-state above 3,650 ng/mL (or AUC[0-24] above 87,600 ng.hr/mL); and
- No subject with mean $C_{avg}$ at steady-state below 200 ng/mL (or AUC[0-24] below 4,800 ng.hr/mL).

$C_{avg}$ was the exposure parameter used in studies with POS oral suspension and therefore this was the major bridging PK parameter. In addition to the $C_{avg}$ as the major bridging parameter, the $C_{min}$ is taken into account and evaluated against the $C_{avg}$ requirements.
4. Discussion

Remarkable difference in $C_{\text{max}}$

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Question 2

Do you have an explanation for the difference in $C_{\text{max}}$ between day 2 and day 7?

1. The further in ECMO therapy, the more pronounced the influence on drug concentrations will be

2. The difference is due to the loading dose on day 1

3. On the late day, the patient was dialysed

4. More research is needed to answer this question
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4. Discussion

Comparison with Cornely et al.

- Posaconazole exposure ≈ Cornely et al.
- Variable exposure might be explained by patient- and disease-specific characteristics

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<tr>
<td>Cornely et al.</td>
<td>Day 10 or 14</td>
<td>36.10</td>
<td>3.28</td>
<td>1.09</td>
<td>1.50</td>
</tr>
<tr>
<td>(J Antimicrob Chemother 2017; 72:3406-3413)</td>
<td>Hematology</td>
<td></td>
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Cornely et al. (J Antimicrob Chemother 2017; 72:3406-3413)
4. Discussion

- $C_{\text{min}}$ and $C_{\text{averg}}$ within the provided target ranges
- Exposure $\approx$ Cornely et al.

Based on this patient no dramatic influence on posaconazole concentrations is observed

More research needed
THANK YOU FOR YOUR ATTENTION