Fluconazole dose adjustment by PK/PD approach for drug effectiveness in ICU septic burned patients with fungal infection caused by Candida glabrata MIC 32 mg/L

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Background

- Burned patients are easy target for fungal colonization/infection due to normal skin barrier disruption and immunocompromised state associated with burn lesions.
- Systemic inflammatory response syndrome in critically ill burned patients leads to altered pharmacokinetics affecting drug exposure.
- Higher than usual doses seems to be necessary even for typical susceptible microorganisms.
- PK/PD approach contributes to optimization and individualization of antimicrobial therapy.

Objectives

To investigate fluconazole empirical usual dose regimen attainment to PK/PD recommended target.

Results

Criticallly ill burned patients characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age (years)</th>
<th>ADW (kg)</th>
<th>IBW (kg)</th>
<th>TBSA (m²)</th>
<th>*BMI (kg/m²)</th>
<th>Burned TBSA (%)</th>
<th>Burn type</th>
<th>MV IL</th>
<th>SAPS-3</th>
<th>Surgery (%)</th>
<th>ICU LOS (days)</th>
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</table>

| Median  | 4F/4M | 35          | 70        | 63       | 1.81      | 24           | 46              | ST1E      | 7/8   | 61      | 6           | 55             |

| (IQR)   | (2-42) | (64-71)      | (54-76)   | (1.71-1.84)| (23-26)   | (46-51)       | (55-65)      | (5-13)   |

- ADW: actual body weight; IBW: ideal body weight; TBSA: total body surface area; BMI: body mass index; MV: mechanical ventilation; IL: inhalation lesion; SAPS-3: Simplified Acute Physiology Score 3; ICU LOS: intensive care unit length of stay; ST1E: interquartile range.

No statistical difference was observed in median serum creatinine, creatinine clearance, C-reactive protein, leukocytes/neutrophil cell count and pharmacokinetics parameter between empirical and adjusted set.

Total body clearance seems to be unchanged compared to healthy volunteers. There was a significant linear correlation between creatinine clearance and total body clearance.

Important changes were observed in volume of distribution and biological half-life, both reduced about three times in these burn patients compared with data reported in healthy volunteers.

Casuistry and Methods

- Inclusion criteria:
  - Burned patients in septic shock with use of vasopressor drug
  - Confirmed infection by Candida glabrata
  - Fluconazole therapy ≥72 hours
- Exclusion criteria:
  - Neutropenia and renal impairment/renal replacement therapy
- PK/PD was investigated in two settings: after empirical usual dose (200 mg q12h) and after adjusted dose (400 mg q12h).
- Drug serum concentration was measured in blood sampling at the end of one-hour pump infusion, two hours after infusion (3rd hour) and before the next dose (12th hour) by HPLC-UV.
- PK/PD approach was performed based on the area under the concentration-time curve over 24-hours (AUC_0-24). Predictive index for drug effectiveness AUC_0-24/MIC>25 was considered.

There was a significant linear correlation between fluconazole daily dose and AUC_0-24:

An increase of fluconazole daily dose from 5.7 to 11.4 mg/kg was necessary to achieve PK/PD target according to antifungal therapy individualization for Candida glabrata MIC 32 mg/L.

Conclusion

- Fluconazole pharmacokinetics is altered in critically ill burn patients with impact on desired outcome.
- Dose adjustment was required for target attainment against Candida glabrata (MIC 32 mg/L) and clinical cure for all patients.
- Drug serum measurements and PK/PD approach improve effectiveness in burn patients by real time therapy individualization.

Disclosure

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