Pharmacokinetics of voriconazole and posaconazole administered in experimental models of disseminated scedosporiosis with cerebral involvement

LELIEVRE B(1, 2), ABBARA C(1, 2), GODON C(2), FEREC S(1), TURCANT A (1, 2), BOUCHARA JP(2), DIQUET B(1, 2).

(1) Service de Pharmacologie-Toxicologie et Centre de Pharmacovigilance, CHU d'Angers, Angers, France
(2) l'UNAM Université, Groupe d'Etude des Interactions Hôte-Pathogène (EA 3142), Angers, France.
Context

- Intracerebral diffusion of molecules
  - Presence of the blood brain barrier
  - Activity of the efflux pumps
- Difficult to evaluate
- PK/PD modeling is needed on the basis of data obtained in animal experiments
Scedosporiosis with cerebral involvement

*Scedosporium apiospermum:*
A soil saprophyte fungus causing

- Localized infections (mycetomas, bone or joint infections, keratitis, …)
- Pulmonary infections likely though to result from inhalation of conidia
- Disseminated infections with cerebral involvement
  - Immunocompetent patients: near drowning
  - Immunosuppressed patients: pulmonary transplant recipients, …

Cases of meningitis => fatal outcome until 90ies. Important progress in patient management with the recently available triazole drugs
Scedosporiosis with cerebral involvement

Objective

- Influence of the disease and of the immune status on the pharmacokinetics of the antifungal drugs?

Experimental study

- Kinetic study of blood and CSF concentration of VRC and PSC in two rat models mimicking the two clinical contexts of cerebral scedosporiosis
- An unique dose of VRC and PSC, corresponding to the effective dose in these models (doubling of survival time, no neurological sequelae)
# Study design

<table>
<thead>
<tr>
<th></th>
<th>Immunocompetent</th>
<th>Immunosuppressed</th>
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<tbody>
<tr>
<td><strong>Male Sprague Dawley rats (12 week-old)</strong></td>
<td></td>
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<tr>
<td><strong>Immunosuppressive treatment</strong></td>
<td>/</td>
<td>Cyclosporine (D-2, D-1, D+1, D+3…)</td>
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<tr>
<td><strong>Size of the inoculum</strong></td>
<td>$10^6$ spores (IV) at day 0</td>
<td>$10^5$ spores (IV) at day 0</td>
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<td><em>(Scedosporium apiospermum strain IHEM 3817)</em></td>
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<tr>
<td><strong>Antifungal treatment</strong></td>
<td>VRC (30 mg/kg/d, IV) or PSC (50 mg/kg/d, oral route) at day 1</td>
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</tbody>
</table>
Study design

- Kinetic study
  - Posaconazole: 14 sampling times, between 0 and 168 h
  - Voriconazole: 19 sampling times, between 0 and 48 h
  - 3 rats per sampling time

- Sampling: blood, cerebrospinal fluid (CSF) and organs (brain) harvested after sacrifice

- Analysis by LC-MS/MS
  Sample preparation: protein precipitation

- Statistical analysis using Student’s t test ($\alpha < 5\%$)
Discussion

- Difference in route of administration: i.v. versus oral route

- Differences between CSF and blood concentrations
  - Lag time
  - Ratio $C_{\text{max}}$ CSF/Plasma: 0.5-0.6 for VRC, 0.01-0.05 for PSC


- Influence of the immune status, more than the disease
Conclusion

- Differences in the kinetics of voriconazole and posaconazole concentrations in blood and CSF greatly influenced by the immunodeficiency
  - Immune status of the host
  - or effect of the immunosuppressive treatment
    - Inhibition of CYP3A4
    - Inhibition of Pgp

- Relation between CSF and brain concentrations of triazole antifungals

- Concentrations in blood, CSF and brain => PK-PD modeling