Monitoring of Voriconazole (VRC) Blood Levels for Prevention of Serious Neurological Adverse Events (SNAE)

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Background: Voriconazole (VRC) is a widely used broad-spectrum antifungal agent. Non-linear pharmacokinetics, polymorphism of cytochrome CYP2C19, drug interactions and hepatic dysfunction may result in inter- and intra-individual variations of VRC blood levels. We reported SNAE probably associated with prolonged VRC overdosing (tough blood levels higher than 5.5 mg/L during more than 7 d) (ICAAC 2005, M-2164). This observation suggested that VRC dose adjustment based on monitoring of blood levels may help to prevent SNAE.

Objective: To prospectively evaluate the utility of monitoring VRC blood levels for prevention of SNAE.

Methods: VRC trough blood levels were measured by HPLC during the first week of therapy in 25 consecutive treatment courses during 2005. VRC dosing was adjusted if VRC trough blood levels were >5.5 mg/L. Clinical follow-up included surveillance for adverse events (NCI criteria). Occurrence of SNAE during VRC therapy in 2004 (no prospective dose adjustment based on VRC blood levels) and 2005 (prospective dose adjustment) was compared.

Results: Indications for VRC therapy were aspergillosis (60%), candidiasis (16%), and suspected mycosis (24%). Median VRC dose was 4 mg/kg bid (range 1.3–5.7). Median number of VRC trough blood levels measurements/treatment course was 2.5 (range 1–5). Median days to first measurement after starting VRC therapy were 2 (2–7). Nine pts (37%) presented transient self-limiting visual disturbances/hallucinations. Two patients (8%) presented severe hepatotoxicity. Occurrence of SNAE in 2004 and 2005 is compared in the table.

<table>
<thead>
<tr>
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<th>2004</th>
<th>2005</th>
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<tr>
<td>Pts with VRC trough level &gt;5.5 mg/L</td>
<td>8/32 (25%)</td>
<td>5/25 (20%)</td>
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<tr>
<td>Median days &gt;5.5 mg/L (range)</td>
<td>12.5 (6–30)*</td>
<td>4 (4–7)</td>
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<tr>
<td>SNAE</td>
<td>4/32 (12%)</td>
<td>0/25 (0%)</td>
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*P = 0.05.

Conclusions: These prospective data corroborate our preliminary report that rapid dose adjustment in patients with VRC blood levels exceeding 5.5 mg/L may help to prevent serious neurological adverse events. Further observations are needed to confirm this finding.

Sacral Zoster with Secondary Dissemination and Urinary Retention: A Case Report and Review of the Literature

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Background: A 52 year old patient with low grade non Hodgkin lymphoma known since 2000 had received conventional chemotherapy until 2002. Upon lymphoma progression, he underwent 5 cures of fludarabine/rituximab/cyclophosphamide chemotherapy from September 2004 to January 2005 that resulted in complete remission. Two months before admission, total lymphs were 456 cells/mm³, CD4+ 115 and CD8+ 228. Ten days before admission, a crop of painful vesicles appeared on the right buttock, in a 54 crescent distribution. A few days later, disseminated vesicles started to appear on the whole body. Oral valaciclovir was initiated but vesicles continued to appear which led to the admission of the patient three days later. The physical including the neurological exam, was unremarkable except for cutaneous findings. Blood cell count and chemistry were unremarkable. Aciclovir (2 x 10 mg/kg/d) was administered. Within 3 days, no new lesions were noticed, but the S4 right dermatome presented as a shallow confluent ulceration with a fibrinous exudate in the intergluteal area. Five days after admission, the patient presented a urinary retention that required urethral catheterisation. Absent right achillean and patellar reflexes, and paresthesias on the right thigh and buttock were observed. Retrospectively, he mentioned that he had had difficulties with micturition since the appearance of the vesicles.

Conclusions: Urinary retention is a well described complication of sacral zoster. Published case reports suggest that in a majority of cases, bladder function recovers within a few weeks. This condition should thus be treated by transient urethral catheterization.

Long-term Management and Safety of Oral Posaconazole for Progressive Zygomycosis in a Pediatric Oncology Patient Following Ambisome Intolerance

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Background: Rhino-orbitocerebral mucormycosis is known to cause fatal infection and severe morbidity in immunocompromised patients. The feasibility and safety of high dose posaconazole in a child
with leukemia and extensive mucor infection was evaluated.

Methods: Pre-B acute lymphoblastic leukemia was diagnosed in a 3-year-old male in June 2002. During induction treatment he presented with fever, periorbital swelling and a black lesion on his hard palate with subsequent pathology positive for invasive zygomycosis. MRI of the head and orbits showed extensive bony destruction of frontal, maxillary, sphenoid and nasal bone with development of infiltrating masses within the orbits. After extensive surgical resection and debridement, he started on amphotericin B and shortly after switched to liposomal amphotericin. MRI of the head showed progression of the infection and frontal lobe cerebritis consistent with direct spread of the disease during treatment with high dose ambisome. The patient developed hypertension, elevated creatinine, pending renal failure; treatment was switched from ambisome to posaconazole on compassionate basis in December 2002, and 7 months later ambisome was added three times a week. The patient has continued on posaconazole for the past three years with days of interruptions due to chemotherapy, specifically, vinca alkaloid. At 2 years into treatment the patient suffered leukemia relapse.

Results: The patient was successfully managed with high dose posaconazole 200 mg three times a day for a period of 7 months with no major toxicity and stable disease in spite of being treated with high dose chemotherapy. Patient also tolerated the combination of ambisome three times a week with high dose posaconazole fairly well. In spite of relapse for leukemia and intensification of chemotherapy we were able to continue ambisome and posaconazole and keep the mucor under control. MRI of head two years post treatment showed resolution of most of the previous abnormal findings, and a limited biopsy did not show any fungal elements. Currently the patient is in second remission for leukemia and on maintenance chemotherapy with 200 mg posaconazole two times a day.

Conclusion: Our case is a good example of a very complicated case of mucor infection with leukemia. We were able to manage both issues of leukemia and mucor with no major morbidity, with acceptable level of toxicity of mild to moderate facial disfiguration while keeping bilateral vision intact.

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A Prospective French National Survey to Assess Renal Safety of Amphotericin B lipid Complex and Liposomal Amphotericin B

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Purpose: Lipid-based amphotericin B formulations (LF) have been recommended to treat patients suffering from renal insufficiency. We report a prospective multicentre survey to assess renal function in adult patients treated for fungal infections with LF: Abelcet® (ABLC) and Ambisome® (L-Amb).

Description: 88 patients (43 F, 45 M) with a mean age of 49.6 ± 14 years were included and evaluable for renal safety. 44% of patients had neutropenia <500mmº. 60 patients were treated with ABLC (median dose: 4.8 mg/kg/day) and 28 patients with L-Amb (median dose: 3.3 mg/kg/day). The mean duration of treatment was 13.5 ± 8 days for ABLC and 15 ± 11 days for L-Amb. 68% of the patients received 2 or more nephrotoxic drugs (72% for ABLC; 61% for L-Amb).

Results: No significant change occurred between median serum creatinine level at baseline (81.3 μmol/L [38.0; 465.0], 88.8 μmol/L [42.0; 356.0]) and at end of therapy (115.0 μmol/L [45.0; 241.6], 106.0 μmol/L [31.0; 363.0], respectively, for ABLC and L-Amb. No significant change occurred between median creatinine clearance at baseline (94.6 and 85.2 ml/min) and end of therapy (60.4 and 71.6 ml/min), respectively, for ABLC and L-Amb. In the group of 26 patients with renal insufficiency prior to treatment, no significant difference was found between median creatinine level and creatinine clearance at baseline.