Visual Hallucinations Associated with High Posaconazole Concentrations in Serum

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Posaconazole is a triazole used for the prevention and treatment of fungal infections. Unlike other mold-active azoles, posaconazole is generally well tolerated. Dose-dependent toxicity was not identified during the registration trials of the intravenous and tablet formulations, and levels in serum as high as 3.35 μg/ml were observed (1, 2). We present herein the first case of visual hallucinations and neurological disturbances associated with extremely high levels of posaconazole in a patient undergoing treatment for chronic pulmonary aspergillosis (CPA).

The patient is a 37-kg, 69-year-old female known to have chronic obstructive pulmonary disease. She was diagnosed with CPA in March 2014 and was treated with itraconazole at 200 mg per os (p.o.) twice a day (BID) for 11 months. In May 2015, voriconazole at 200 mg p.o. BID was initiated for treatment of a clinical and radiological relapse of her disease. After 1 week of voriconazole therapy, she presented to our hospital with acute complaints of disturbing visual hallucinations, including menacing miniature people. A medication review revealed no known drug-drug interactions associated with hallucinations. Posaconazole levels were not measured, but a diagnosis of voriconazole-associated visual toxicity was made, her therapy was changed to posaconazole in oral suspension (200 mg p.o. four times a day [QID]), and her visual hallucinations resolved over 10 days.

One month later, the posaconazole suspension was changed to the tablet formulation at 300 mg p.o. daily for improved tolerability. Five days later, she developed an acute recurrence of similar visual hallucinations, altered mental status, and symptoms of parkinsonism. A medication review revealed no known drug-drug interactions associated with hallucinations. Posaconazole trough level was 10.10 μg/ml, which is, to our knowledge, the highest reported level of this agent in serum. Posaconazole tablets were discontinued, and her symptoms resolved with decreasing levels of posaconazole in serum (Table 1). Posaconazole suspension at 200 mg p.o. BID was initiated without symptom recurrence.

Visual and neurological disturbances are well-described adverse effects associated with voriconazole (3, 4). Although the exact mechanism remains unclear, it has been suggested that voriconazole-mediated inhibition of CYP46A1 leads to reduced 24S-hydroxycholesterol levels in retinal and neural cells, disrupting cholesterol homeostasis and membrane function (5). Alternatively, data from mouse models suggest that visual disturbances may result from voriconazole-mediated inhibition of transient receptor potential cation subunit M (TRPM1 and TRPM3) channels within retinal and neural cells (6). Posaconazole also binds CYP46A1 and may therefore also inhibit these pathways (7, 8).

Table:<br>
<table>
<thead>
<tr>
<th>Date</th>
<th>Antifungal treatment</th>
<th>Posaconazole level (μg/ml)</th>
<th>Feature(s) of toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>21 May 2014</td>
<td>Itraconazole (200 mg p.o. BID) started</td>
<td>10.10</td>
<td>Visual hallucination, cogwheeling, postural hypotension, dysphagia, cognitive impairment</td>
</tr>
<tr>
<td>26 February 2015</td>
<td>Itraconazole stopped</td>
<td>5.47</td>
<td>Improving symptoms</td>
</tr>
<tr>
<td>4 June 2015</td>
<td>Voriconazole (200 mg p.o. BID) started</td>
<td>1.17</td>
<td>No neurological signs or symptoms</td>
</tr>
<tr>
<td>11 June 2015</td>
<td>Voriconazole (200 mg p.o. BID)</td>
<td>0.64</td>
<td>No neurological signs or symptoms</td>
</tr>
</tbody>
</table>

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Table: Dates and treatments for a 37-kg, 69-year-old female with CPA

<table>
<thead>
<tr>
<th>Date</th>
<th>Antifungal treatment</th>
<th>Posaconazole level (μg/ml)</th>
<th>Feature(s) of toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>13 August 2015</td>
<td>Posaconazole tablets (300 mg p.o. daily)</td>
<td>10.10</td>
<td>Visual hallucination, cogwheeling, postural hypotension, dysphagia, cognitive impairment</td>
</tr>
<tr>
<td>20 August 2015</td>
<td>Posaconazole held</td>
<td>5.47</td>
<td>Improving symptoms</td>
</tr>
<tr>
<td>28 August 2015</td>
<td>Posaconazole held</td>
<td>1.17</td>
<td>No neurological signs or symptoms</td>
</tr>
<tr>
<td>29 August 2015</td>
<td>Posaconazole suspension (200 mg p.o. BID) started</td>
<td>0.64</td>
<td>No neurological signs or symptoms</td>
</tr>
</tbody>
</table>
studied for tolerability, although a toxicity-exposure relationship has yet to be established (13). Thus, patients receiving new formulations of posaconazole should be monitored for visual, CNS, and other novel toxicities, and therapeutic drug monitoring should be performed upon suspicion of toxicity and in patients with low body mass.

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REFERENCES


