Published in final edited form as:

Pediatr Blood Cancer. 2015 September ; 62(9): 1682. doi:10.1002/pbc.25568.

Suspected Posaconazole Toxicity in a Pediatric Oncology Patient

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To the Editor

We report a case of posaconazole toxicity in a 13 year old female with an osteosarcoma-like tumor involving the maxillary sinus. The patient underwent an upfront resection of her primary tumor and subsequently received systemic therapy with cisplatin, doxorubicin, and methotrexate. Inability to achieve a complete surgical excision led to radiation of the primary tumor bed. Her clinical course was further complicated by disseminated candidiasis and hemophagocytic lymphohistocytosis, and after completion of all cancer-directed therapy, she also developed a *Coniothyrium fuckelii* sinus infection. As there are limited data for *in vitro* sensitivities for *Coniothyrium fuckelii*, she was initiated on broad antifungal therapy with voriconazole and liposomal amphotericin B, along with sinus debridement. After significant clinical improvement, she was transitioned to posaconazole suspension 400 mg BID. After 3 days of inpatient treatment with posaconazole suspension, she was inadvertently prescribed posaconazole delayed release (DR) tablets (400 mg BID) for outpatient treatment.

Approximately 2 weeks after discharge, she developed fatigue, decreased appetite, and musculoskeletal pain. Serum chemistries were unremarkable except for a potassium of 2.7 mEq/L and oral potassium supplements were prescribed. In the ensuing weeks, she developed worsening nausea, fatigue, bone pain, and decreased enteral intake. In addition to continued hypokalemia (3.1 mEq/L), she developed progressive anemia as her hemoglobin dropped from 9.1 g/dL to 8.3 g/dL. Because of her minimal enteral intake, there was concern for recrudescence of her disseminated candidiasis due to inadequate posaconazole

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absorption. Admission for further diagnostic evaluation and initiation of intravenous antifungals was considered. However, review of her medications revealed she had been inadvertently started on posaconazole DR tablets upon her discharge from the hospital 2 months prior and thus there was concern her clinical presentation was consistent with posaconazole toxicity. She was instructed to stop taking the drug and a posaconazole level drawn at a clinic visit 3 days after her last dose was 9.5 mcg/mL. The patient's symptoms resolved over one week's time.

Posaconazole was initially formulated as a suspension in 2006. The suspension is well known to have poor absorption and it is recommended that it be administered with a full meal, liquid nutritional supplement, or acidic carbonated beverage.[1] In November 2013, posaconazole DR tablets were approved at a dose of 300 mg BID for 2 doses, then 300 mg daily for prophylaxis of fungal infections in patients ≥ 13 years of age.[1] Due to improved absorption, the DR tablet formulation achieved an AUC approximately 4 times that of posaconazole suspension dosed at 400 mg BID.[1] This improved absorption and different dosing regimen poses a risk for posaconazole toxicity, which was highlighted in a recent Institute of Safe Medication Practices newsletter.[2] To help prevent future errors, the Computerized Physician Order Entry system at our institution was updated to include DR tablets; dosing defaults to 300 mg daily with a maximum dose alert of 300 mg. The hospital's formulary also now highlights dosing differences between formulations. Practitioners prescribing posaconazole DR tablets should be aware of specific dosing recommendations for this formulation and the potential for toxicity presenting with symptoms that can include fatigue, nausea, anorexia, hypokalemia, anemia, and musculoskeletal pain.

References

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2. Institute for Safe Medication Practices Newsletter. Posaconazole dose depends on dosage form. May 22.2014