ISMP Adverse Drug Reactions

Sorafenib-Induced Thyroid Storm

Ceftaroline-Induced Eosinophilic Pneumonia

Imatinib-Induced Osteonecrosis of the Tibia

Visual and Auditory Hallucinations With Citalopram

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The purpose of this feature is to heighten awareness of specific adverse drug reactions (ADRs), discuss methods of prevention, and promote reporting of ADRs to the US Food and Drug Administration's (FDA's) MEDWATCH program (800-FDA-1088). If you have reported an interesting, preventable ADR to MEDWATCH, please consider sharing the account with our readers. Write to Dr. Mancano at ISMP, 200 Lakeside Drive, Suite 200, Horsham, PA 19044 (phone: 215-707-4936; e-mail: mmancano@temple.edu). Your report will be published anonymously unless otherwise requested. This feature is provided by the Institute for Safe Medication Practices (ISMP) in cooperation with the FDA's MEDWATCH program and Temple University School of Pharmacy. ISMP is an FDA MEDWATCH partner.

SORAFENIB-INDUCED THYROID STORM

A 72-year-old male has a history of stage II renal clear cell carcinoma, atrial fibrillation, and a radial nephrectomy. The patient remained disease free until 9 years after nephrectomy when he manifested metastatic disease. He had been receiving amiodarone for atrial fibrillation for 1 year before his metastatic cancer diagnosis, but it was stopped preemptively to prevent drug interactions before the initiation of tyrosine kinase inhibitor (TKI) treatment. The patient received pazopanib (*Votrient*) for 6 months when, based on disease progression, he started receiving sorafenib (*Nexavar*) 400 mg twice daily. The patient deteriorated after 2 to 3 weeks of therapy and progressed over 5 weeks with anorexia, diaphoresis, fatigue, tremors, diarrhea, and intermittent confusion.

After 8 weeks of sorafenib therapy, the patient was hospitalized with worsening symptoms of atrial fibrillation. He was agitated and had a pulse of 137 bpm. He had a nonenlarged, nonnodular, nontender

thyroid gland and a fine resting tremor. He had markedly abnormal thyroid function tests (TFTs) with an undetectable thyroid stimulating hormone (TSH) of less than 0.008 μ IU/mL, elevated free T4 (fT4) of 4.06 ng/dL (reference range, 0.89 to 1.76 ng/dL), T4 of 19 μ g/dL (reference range, 4.5 to 10.9 μ g/dL), and mildly elevated free T3 (fT3) of 4.4 pg/mL (reference range, 2.3 to 4.2 pg/mL). Thyroglobulin was elevated at 115 ng/mL (reference range, 1.6 to 59.9 ng/mL), whereas antithyroglobulin, antithyroid peroxidase, and thyroid-stimulating immunoglobulin were undetectable. The patient had a thyroid ultrasound that revealed a heterogenous and atrophic right thyroid lobe with no focal lesions. He was diagnosed with thyroid storm and treated with high-dose propylthiouracil, hydrocortisone, and propranolol. The patient's confusion persisted and his atrial fibrillation remained poorly controlled with intravenous diltiazem and a beta blocker. Three days after admission, the patient had a cardiac arrest in the setting of aspiration and died.

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The authors discussed that the 4 TKIs on the market – sunitinib (*Sutent*), sorafenib (*Nexavar*), pazopanib (*Votrient*), and axitinib (*Inlyta*) – are associated with TKI-induced thyroid dysfunction. Hypothyroidism is generally associated with sunitinib, with 30% of patients requiring thyroid hormone replacement therapy. The lowest reported incidence of patients developing hypothyroidism is associated by pazopanib, and there are currently no data available on TSH trends in patients receiving pazopanib.

The patient had normal baseline TFTs and presented with thyroid storm 8 weeks after initiating sorafenib. He had no significant drug-drug interactions between sorafenib and other medications, and he had not received iodine-containing contrast after initiating sorafenib. The authors theorize that several mechanisms may explain TKI-induced thyroid dysfunction. One mechanism could be VEGF inhibition that causes capillary regression to several organs with the greatest regression to the thyroid gland, which suggests that the thyroid gland may be particularly sensitive to inhibition. A second mechanism is the possible blocking of iodine uptake by TKIs. Clinically, TKI-induced thyroid dysfunction does not seem to be mediated by autoimmune mechanisms, given that antithyroid peroxidase activity and antithyroglobulin antibodies have been found to be negative in most patients with thyroid dysfunction. The authors propose that more than one mechanism causes TKI-induced thyroid dysfunction, given that some patients develop thyroiditis with or without symptoms of hyperthyroidism, whereas others do not. It is also likely that the incidence of thyrotoxicosis is underestimated, because the symptoms are nonspecific and overlap with other TKI-induced adverse effects.

The authors state that optimal therapy for TKI-induced thyrotoxicosis is unknown. If thyroiditis is the cause for most cases of TKI-induced thyrotoxicosis, initiating antithyroid medication is unlikely to be helpful. Although one previous case report demonstrated benefit with glucocorticoids, the current patient did not benefit from glucocorticoids. Guidelines for thyroid function monitoring have not been developed, but several authors have suggested monitoring TSH for the first 4 months of therapy, given that thyroid dysfunction tends to occur early. Patients with preexisting thyroid dysfunction may require closer monitoring, and patients who discontinue therapy may also require monitoring given that thyroid dysfunction can resolve once therapy is stopped.

The authors surmise that sorafenib-induced thyroid storm may be under-recognized, because the

symptoms of thyroid storm can overlap with symptoms of other TKI-related toxicities. Monitoring is essential; thyroid storm requires prompt recognition and treatment because of the high mortality associated with this condition.

Haralddottir S, Li Q, Villalona-Calero MA, et al. Case of sorafenib-induced thyroid storm. *J Clin Oncol*. 2013;31(16):e262-e264.

CEFTAROLINE-INDUCED EOSINOPHILIC PNEUMONIA

A 46-year-old male who was morbidly obese (body mass index [BMI] = 56) with type II diabetes mellitus underwent a spinal surgery and developed a surgical site infection and bacteremia secondary to methicillin-resistant *Staphylococcus aureus* (MRSA). The vancomycin MIC for the MRSA isolate was 2 mcg/mL; based on this information and the patient's body weight (173 kg), ceftaroline (*Teflaro*) was initiated. Pathogen susceptibility to ceftaroline was confirmed (MIC of 0.75 mcg/mL) and the patient was discharged to an extended care facility with ceftaroline 600 mg intravenously every 8 hours for a planned 6 weeks of therapy.

The patient developed shortness of breath, dry cough, and hypoxemia on day 39 of ceftaroline therapy. He was hospitalized and was noted not to have fever or chills. Vital signs on admission were temperature of 97.5°F, heart rate 105 bpm, respiratory rate 32 beats/min, blood pressure 125/66 mm Hg, and an oxygen saturation of 90% while receiving 5 L of oxygen via nasal cannula. Contributory lab data included an elevated white blood count of 12,000/mm³ (reference range, 4.1-10.9/mm³) with an absolute eosinophil count of 1,500/mm³ (reference value, < 350/mm³). Chest x-ray showed bilateral patchy nodular infiltrates, and a CT scan of the chest revealed diffuse bilateral infiltrates with bilateral hilar and mediastinal adenopathy. The patient's history included no history of asthma, and he was a lifelong nonsmoker. He had not started any new medications, and there was no travel history suggestive of environmental exposure since the patient had been discharged to an extended care facility to receive his intravenous ceftaroline therapy.

Upon admission, the patient's ceftaroline was discontinued and aztreonam and tigecycline were initiated as presumptive therapy for suspected pneumonia caused by ceftaroline-resistant pathogens. The patient's respiratory status worsened over the next 48 hours, and he required noninvasive ventilation. A broncho-alveolar lavage (BAL) was performed and demonstrated 16% eosinophils, 62% neutro-

phils, and 20% lymphocytes. Eosinophilic lung disease can be identified by the presence of an increased number of eosinophils in the lung or BAL fluid in a patient with pulmonary symptoms or infiltrates on chest x-ray. Based on the findings, ceftaroline-induced eosinophilic pneumonia was suspected, and the patient was initiated on intravenous methylprednisolone. He experienced significant improvement over the next 24 hours. The patient was then weaned off of oxygen; after an 8-day hospital stay, he was discharged with a prednisone taper as well as an extended course of doxycycline as a follow-up therapy for his MRSA spine infection.

The authors review the possible mechanism of drug-induced eosinophilic pneumonia. The mechanism is not well understood, but interleukin-5, which is produced by T-helper cells, is the main cytokine promoting eosinophil production. The abundance of macrophages in the lung could result in large local production of interleukin-5 with the consequence of preferential accumulation of eosinophils. Because ceftaroline has significant penetration into the lungs, the prolonged use of high-dose ceftaroline may result in persistent and possibly increased exposure to lung tissue macrophages. It is important to note that the patient in this case received ceftaroline 600 mg every 8 hours; ceftaroline has been reported to cause peripheral eosinophilia when administered for an extended duration (up to several weeks). Ceftaroline was administered in clinical trials at a dose of 600 mg every 12 hours for up to 14 days.

The authors caution that health care providers should be alert for patients who develop respiratory symptoms in combination with new pulmonary infiltrates with or without peripheral eosinophilia in patients treated with ceftaroline. Ceftaroline-induced eosinophilic pneumonia should then be suspected.

Desai KR, Burdette SD, Polenakovich HM, et al. Ceftaroline-induced eosinophilic pneumonia. *Pharmacotherapy*. 2013;33(7):e166-e169.

IMATINIB-INDUCED OSTEONECROSIS OF THE TIBIA

A 61-year-old female was diagnosed with metastatic gastrointestinal stromal tumor (GIST) and was initiated on imatinib (*Gleevec*) four 100 mg capsules daily. After 3 months of treatment, partial response was documented as assessed by CT scan. At 6 months, however, the patient complained of bone pain in both lower extremities, with limping gait and limited range of motion. A whole-body bone scan and an MRI were completed, and they revealed osteonecrosis of the tibia.

A pharmacokinetic assessment of the patient indicated that the blood level of imatinib was 2,020 ng/mL. The patient had no evidence of an underlying metabolic bone disorder. Imatinib was discontinued and replaced with nilotinib (*Tasigna*). The patient's bone pain subsided immediately, and she recovered her range of motion. Follow-up bone scans completed 2 and 6 months after the discontinuation of imatinib indicated a reduction in the severity of osteonecrosis.

A subsequent CT scan performed 6 months after the start of nilotinib demonstrated GIST disease progression. Imatinib 400 mg daily was restarted; after 1 month of treatment, the blood level of imatinib was 4,040 ng/mL. A subsequent CT scan revealed a partial response after the patient had taken imatinib for 3 months; however, the patient experienced bone pain in both lower extremities. A bone scan revealed increased osteonecrosis of the tibia.

The authors point out that imatinib is considered the standard first-line agent for the treatment of unresectable or metastatic GIST. Common adverse effects (diarrhea, edema, asthenia, myalgia, and skin reactions) are most often mild and manageable. Musculoskeletal complaints are a common adverse effect of imatinib therapy, affecting approximately 40% of patients. Musculoskeletal adverse effects are typically mild to moderate in severity and manifest as muscle cramps and/or pain, primarily occurring in the hands, feet, calves, and thighs with a varying pattern, frequency, and severity. Bone pain and arthralgia have been reported in up to 14% of patients with GIST who are receiving 400 mg of imatinib daily. The associated symptoms (which can be severe, disabling, and strikingly asymmetric) primarily affect the femur, tibia, hip, and knee. Imatinib administration may be associated with hypophosphatemia and hyperphosphaturia and with changes in bone and mineral metabolism, which is possibly mediated by inhibition of osteoclast function.

The authors summarize that the temporal relationship suggests that the patient's osteonecrosis was induced by imatinib; osteonecrosis of the tibia with decreased perfusion occurred a few months after imatinib therapy was initiated. The condition improved after the drug was discontinued and rapidly worsened after treatment was resumed. Although extensive clinical experience supports the safe use of imatinib, the current case report suggests that imatinib may cause osteonecrosis of the tibia in a small proportion of patients.

Yeh CN, Fu CJ, Yen TZ, et al. Osteonecrosis of the tibia associated with imatinib in metastatic GI stromal tumor. *J Clin Oncol*. 2013;31(16):e248-e250.

VISUAL AND AUDITORY HALLUCINATIONS WITH CITALOPRAM

A 22-year-old male with obsessive compulsive disorder (OCD) and posttraumatic stress disorder (PTSD) sought treatment for insomnia, depressed mood, anhedonia, and disturbing obsessions. The patient did not have a personal or family history of psychotic symptoms. Consumption of legal and illegal drugs as well as at-risk mental states for psychosis or psychotic symptoms were excluded. The patient was initiated on mirtazapine 30 mg daily; however, after 6 weeks of treatment and some improvement of mood and insomnia, his psychiatrist added citalopram (*Celexa*) 20 mg daily, which was increased to 40 mg daily in the second week and to 60 mg daily in the third week. The citalopram 60 mg dose exceeds the recommended dose and was the dose the patient was receiving 3 days prior to his hospitalization.

During the second week of citalopram therapy, the patient experienced auditory and visual hallucinations. He described seeing foreign people in his house who commented on his daily routines and work duties. He also reported seeing three black-coated policemen who were observing and persecuting him on the streets and in his garden. He perceived this as extraordinarily strange and asked for psychiatric inpatient treatment. On admission, his antidepressant medications were stopped and lorazepam 4 mg daily was initiated for agitation and anxiety.

A general physical and neurological examination appeared normal, cranial MRI ruled out structural alterations of the brain, and laboratory tests included urine drug screen and cerebrospinal fluid evaluation to identify specific markers of inflammation. Lab test results did not reveal any abnormalities. Approximately 48 hours after admission, the

patient had a serum level of citalopram of 59 g/μL (reference range, 20-250 g/μL), and mirtazapine was not detectable.

The patient's psychotic symptoms remitted 3 days after the last dose of citalopram. Sertraline 50 mg daily was initiated, and his psychotic symptoms recurred after 4 days of sertraline therapy. Sertraline was discontinued and mirtazapine was restarted at 30 mg daily, and he was tapered off of lorazepam. The patient was discharged. Outpatient treatment of his PTSD and OCD was to be addressed with cognitive therapy as well as mirtazapine.

The authors attribute the observed psychotic syndrome to the speedy dose escalation of citalopram. The assessed serum levels of citalopram do not suggest peak serum levels much exceeding the therapeutic range. Even in acute citalopram intoxications, psychotic symptoms are not regularly described. Sensitive patients seem to develop hallucinatory behavior as a general adverse reaction to selective serotonin reuptake inhibitors (SSRIs). The mechanism of SSRI-induced hallucinations might involve the agonism of 5-HT₂ receptors, the blockade of dopamine reuptake, or the interaction with sigma receptors.

The authors conclude that this case does not completely recommend against the combined administration of mirtazapine and citalopram, which has been described as being beneficial in OCD treatment. They recommend that further investigations should determine whether high-dose SSRI treatment really improves clinical response and whether patients with high sensitivity to secondary psychotic symptoms need slower dose escalations.

Waltereit R, Eifler S, Schirmbeck F, et al. Visual and auditory hallucinations associated with citalopram treatment. *J Clin Psychopharmacol*. 2013;33(4):583. ■