ISMP Adverse Drug Reactions:

Levofloxacin-Induced Neuroexcitation and Hallucinations

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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) 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.

Levofloxacin-Induced Neuroexcitation and Hallucinations

A 2-year-old girl was admitted to the hospital after central line placement prior to receiving a stem cell transplant. She had a history of stage IV neuroblastoma and tolerated her induction therapy well. She had a history of *Klebsiella* sepsis and 2 episodes of neutropenic fever. She did not have any emotional, cognitive, or behavioral disturbances; no previous psychiatric history; and no previous use of psychotropic medication.

On day 1 of her admission, busulfan was initiated and continued until day 5. On day 5, the patient received levofloxacin (Levaquin) prophylaxis according to an oncology protocol for bone marrow transplantation. The patient received levofloxacin daily until the time of engraftment. Other medications the patient had received during this time were acyclovir prophylaxis, fluconazole prophylaxis, ondansetron as needed, lorazepam as needed, aprepitant as needed, cyproheptadine, cholecalciferol, omeprazole, ursodiol, oxycodone as needed, and morphine as needed.

The patient received levofloxacin at 12:12 a.m. and 8:20 p.m. on hospital day 5. Overnight, the patient's mother reported that the patient experienced sleep disturbances with episodes of agitation, disorientation, swatting at things that were not there, and pinching herself. On the sixth day, the patient did not exhibit any behavioral, cognitive, or emotional disturbances during the day. She received levofloxacin at 9:11 a.m. and 10:38 p.m. on day 6. In the evening, she

exhibited agitation, disorientation, psychomotor agitation, aggression, and a change in mood. She was swatting at nurses, pulling on her garments, and crying excessively. She developed tactile hallucinations in which she described bugs crawling on her lower extremities. A psychiatry consult was completed, and the patient was given a provisional diagnosis of delirium. Psychiatry recommended that the patient's exposure to benzodiazepines be limited. The patient's mother noted a history of similar symptoms after the patient had received levofloxacin. Based on this information, the oncology team adjusted the dosing of levofloxacin to an earlier time in the day.

The patient received an autologous bone marrow transplant on hospital day 7. Her second dosage of levofloxacin was adjusted to be administered at 4:00 p.m., and melatonin was given at 9:45 p.m. She did not experience any change in her behavior overnight. On day 8, her second levofloxacin dosage was administered at 6:47 p.m. and her melatonin was given at 8:03 p.m. The patient awoke overnight with a brief episode of visual and tactile hallucinations. This episode was short and she exhibited less agitation and aggression overall.

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On hospital days 9 to 13, the patient's evening dosage of levofloxacin was administered between 2:47 p.m. and 3:45 p.m. Melatonin was not administered on these days. The patient did not exhibit emotional, cognitive, behavioral, or perceptual disturbances. The patient did not have evidence of graft-versus-host disease or acute rejection.

Husain et al¹ review 2 possible mechanisms by which fluoroquinolones may cause excitatory effects. The first mechanism may be due to the fluoroquinolones blocking the binding of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA); however, levofloxacin has a relatively low binding affinity for GABA. The second mechanism may occur via fluoroquinolones binding to and activating N-methyl-D-aspartate receptors, therefore causing direct neuroexcitation. The patient in this case experienced agitation, confusion, and overt hallucinations when levofloxacin was administered after 8:00 p.m.

Husain et al¹ state, "The fact that neuroexcitation, perceptual disturbance, and behavioral disturbance only occurred with evening levofloxacin dosing and never with the morning dose may suggest a relationship with the sleep-wake cycle, alertness neurocircuitry, or reduced environmental cues to maintain mentation in the evening." The authors conclude, "Recognizing this adverse effect and adjusting the time of levofloxacin administration may alleviate neuroexcitation, thus allowing for continuation of the antibiotic while avoiding delays in care or unneeded diagnostic testing and interventions."

Statin-Induced Muscle Rupture

Ekhardt et al² conducted a study to analyze the occurrence of muscle rupture in 2 European pharmacovigilance databases. The first database is maintained by the Netherlands Pharmacovigilance Center, which has collected reports since 1990. Reports are primarily received from physicians, pharmacists, and consumers, either directly or via pharmaceutical manufacturers. The authors' database search included all reports entered from the start of 1991 up to January 2016. The Netherlands Pharmacovigilance Database contained 15 cases of muscle rupture associated with the use of statins. The 15 cases occurred in 12 males and 3 females. The median age of patients was 63 years, and patients had been receiving a statin therapy for a median time of 19 months.

Details of the muscle ruptures reported in the Netherlands Pharmacovigilance Database are as follows: 4 patients ruptured biceps, 4 ruptured calf muscles, 2 hamstring ruptures, 1 quadriceps rupture, and 4 unspecified. Additional characteristics of the patient cases include 2 patients who had tendon ruptures as well as muscle ruptures, and 4 patients who had their muscle rupture during normal daily activities; however, in 3 patient cases, exercise could have played a role in the muscle rupture. The association of statin use and muscle rupture was disproportionally present in the Netherlands Pharmacovigilance Database with a reporting odds ratio of 23.4% (95% confidence interval [CI], 11.9-46.0).

The second database utilized in this study was EudraVigilance. The EudraVigilance database is a European Union spontaneous reporting system that was established in 2001. This database was established to collect safety reports of adverse drug reactions to medications licensed with the European Union. All reports entered into the database up to January 2016 were evaluated for this study. The EudraVigilance database contained 165 reports of muscle rupture associated with statin use. Of the 165 cases, 11 occurred in patients who did not utilize any other medication besides a statin. These 11 cases were reported with a plausible time of statin exposure, and no alternative factors that could explain the patient's muscle rupture. Eight cases occurred in men and 3 cases occurred in women with the median age in all cases of 57 years. The association of statin use and muscle rupture was disproportionally present in the EudraVigilance database with a reporting odds ratio of 14.6% (95% CI, 12.3-17.2).

Ekhardt et al² point out that there are at least 9 different theories to explain statin-induced myopathy. Regardless of the mechanism responsible for statin-induced myopathy, if there is damage to a considerable proportion of muscle tissue, this may eventually result in muscle rupture. Mild strains may heal quickly on their own with rest, but more severe tears may require surgery and a rehabilitation program. Most patients recover from myopathy within 6 months after statin withdrawal; however, muscle symptoms can linger beyond 14 months. The authors conclude, "Our data suggest that statin-induced muscle rupture can occur in patients receiving statins, also in the absence of intense physical activities."

Mefloquine-Induced Rhabdomyolysis

A 36-year-old black male developed symptoms of malaise, fatigue, and difficulty performing his usual daily activities. He reported the symptoms had started several weeks ago. The patient had recently returned from a trip to Nigeria where he had stayed for 5 weeks. He was taking mefloquine (Lariam) 250 mg once weekly as prophylaxis for malaria. He initiated mefloquine 2 weeks before leaving home, and he was to stop mefloquine 4 weeks after returning home from his trip. The patient had no medical history or medication history other than mefloquine. The patient also did not report any febrile episodes before, during, or after return from his trip to Nigeria.

Physical findings and laboratory results were normal except for a creatine kinase (CK) of 2978 U/L (normal value, ≤ 195 in males), sodium 133 mEq/L (normal value, 135-145 mEq/L), and a modest increase in creatinine 1.24 mg/dL (normal range, 0.9-1.2 mg/dL). The patient received intravenous infusions of normal saline alternated with 5% dextrose at a rate of 300 mL/h for 12 hours. The patient's CK decreased to 641 U/L and his creatinine concentration was 0.97 mg/dL. Serological testing was also negative, which ruled out

malaria infection; hepatitis A, B, and C; dengue fever; and chikungunya.

The patient refused to remain in the hospital but promised to return in 2 days for follow-up. Two days later, his CK had normalized at 176 U/L and his serum creatinine was 0.97 mg/dL. He also reported he felt well and was able to resume his usual activities. The patient was followed for 3 months via telephone calls, and he remained in good health.

Comelli et al³ concluded, "When evaluating a patient returning from a journey or staying in tropical counties, anti-malarial drugs, such as mefloquine, should be considered among the potential causes of rhabdomyolysis, especially in patients complaining for nonspecific symptoms, like malaise and fatigue."

Methimazole-Induced Cholestatic Hepatitis

Zou et al⁴ reported 2 cases of cholestatic hepatitis caused by methimazole (Tapazole). The first case occurred in a 50-year-old female who described a change in urine color, severe pruritus, diarrhea, and weight loss for 8 days. She reported that 8 days prior, she initiated methimazole 10 mg daily and propranolol 10 mg 3 times daily for recently diagnosed hyperthyroidism. She had not received any other medications and did not report abdominal pain, fever, history of alcohol use, or history of liver disease. She demonstrated severe icterus of the sclerae and skin.

Laboratory results revealed an abnormally high free thyroxine (FT₄) of 56.33 pmol/L (normal range, 11-25 pmol/L) and a low thyroid stimulating hormone (TSH) of <0.005 mU/L (normal range, 0.5-5 mU/L). Hepatic function tests revealed a total bilirubin of 105.86 µmol/L (normal range, 3.4-25 µmol/L), direct bilirubin of 54.21 µmol/L (normal range, 0-8 µmol/L), alkaline phosphatase (ALP) of 200 U/L (normal range, 34-104 U/L), gamma-glutamyl transferase (GGT) of 104 U/L (normal range, 0-60 U/L), aspartate aminotransferase (AST) of 17 U/L (normal range, 0-50 U/L), and alanine aminotransferase (ALT) of 120 U/L (normal range, 5-64 U/L). The patient's albumin, prothrombin time, partial thromboplastin time, and blood cell counts were within normal limits. Serology for hepatitis viruses A, B, C, D, and E; Epstein-Barr; and cytomegalovirus were all negative. Autoantibody profiles for primary biliary cirrhosis and autoimmune hepatitis were also negative. An abdominal ultrasound was unremarkable. Treatment with methimazole was stopped, and propranolol therapy was continued for symptomatic relief. The patient's AST, ALT, and bilirubin were nearly normal 4 weeks after methimazole discontinuation. The patient refused thyroidectomy or radioactive iodine treatment for her hyperthyroidism and was started on propylthiouracil 50 mg daily. The patient's thyroid function tests and hepatic function tests normalized after initiation of propylthiouracil therapy.

The second patient was a 42-year-old female who was started on methimazole 30 mg daily for the treatment of hyperthyroidism. Two weeks after starting methimazole,

the patient experienced pruritus that she considered a drug allergy. The patient decreased her methimazole dosage to 15 mg daily and continued to take her medication until her appetite decreased. She presented with severe pruritus after 27 days of methimazole therapy. The patient had no medical history except for hyperthyroidism, and she had no history of alcohol use. She had severe icterus of the sclerae and skin.

Laboratory tests revealed an FT₄ of 24.48 pmol/L and TSH of 0.008 mU/L. Hepatic function test results were total bilirubin of 268.87 µmol/L, direct bilirubin of 116.8 µmol/L, ALP of 353 U/L, GGT of 255 U/L, AST of 105 U/L, and ALT of 135 U/L. Concomitant liver diseases, such as viral hepatitis A, B, C, D, and E, autoimmune hepatitis, and primary biliary cirrhosis, were excluded by serological analysis. The patient's methimazole was discontinued at this time; however, after 2 weeks, the patient had progressive worsening of nausea, anorexia, itching, and jaundice. The patient's total bilirubin peaked at 348.2 µmol/L and direct bilirubin of 262.12 µmol/L. Intravenous methylprednisolone was then administered for 6 days, and her total bilirubin and direct bilirubin both fell to 183.21 µmol/L and 157.9 µmol/L, respectively. The patient was continued on a methylprednisolone taper for the next 16 weeks, and her liver function tests returned to normal.

Zou et al concluded, "In rare cases within the first few weeks of therapy, methimazole can cause severe and reversible cholestatic jaundice. Physicians and patients should be aware of this rare but serious adverse effect. Meanwhile it is essential that patients are informed about the earliest symptoms of serious adverse effects of antithyroid drugs, such as agranulocytosis and hepatic toxicity, and that they are advised to stop taking the drug immediately and contact their physician if such symptoms occur."

Decitabine-Induced Hand and Foot Syndrome

A 61-year-old Caucasian male was diagnosed with acute myeloid leukemia that had been treated with chemotherapy and relapsed twice. The patient was deemed inappropriate for further aggressive chemotherapy. The patient was started on decitabine (Dacogen) 20 mg/m² daily for 5 days. On the third day of decitabine therapy, the patient developed a burning and tingling sensation in his palms. The patient's symptoms did not warrant discontinuation of decitabine therapy, and he received the full 5-day course as prescribed. A few days after his chemotherapy course was complete, the patient progressed to symmetric well-defined swelling and erythema. The patient's erythema was most prominent on the lateral aspects of the fingers and distal fat pads. The patient was evaluated and considered to have grade II hand and foot syndrome (HFS). The patient was not receiving any other medications known to cause HFS or interact with decitabine.

The patient was treated symptomatically with pain control and high-potency topical corticosteroids. The patient's condition did not progress to blistering, ulceration, or desquamation. The rash and the pain improved and gradually resolved over the next week. Ultimately, the patient's functional status deteriorated due to recurrent pneumonia, and he was transitioned to supportive care.

The authors report that HFS is often debilitating and painful and can impair activities of daily living.⁵ HFS is the most common reason for a dosage reduction and/or discontinuation of chemotherapy, thereby limiting the use of potentially effective therapy. A rechallenge of patients with the offending agent utilizing a similar dosage and schedule has led to recurrence of HFS in most but not all patients. A number of chemotherapies have been associated with causing HFS, with the highest incidence (40%-60%) occurring with pegylated liposomal doxorubicin and capecitabine. Other agents that have caused HFS include cytarabine, 5-fluorouracil, docetaxel, sorafenib, and sunitinib. The risk of developing HFS appears to be dose

dependent. The drug formulation and administration schedules that result in sustained serum levels of cytotoxic agents are more likely to result in HFS.

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