ISMP Adverse Drug Reactions

Ipilimumab-Induced Polyneuropathy

Ibuprofen-Induced Allergic-Type Liver Injury

Trimethoprim-Sulfamethoxazole-Induced Immune Thrombocytopenia in Children

Mesna-Induced Fixed Drug Eruption

Digoxin-Induced Ocular Toxicity

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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.

IPIILIMUMAB-INDUCED POLYNEUROPATHY

The authors report 2 cases of ipilimumab (Yervoy)-induced polyneuropathy. Case 1 occurred in a 57-year-old male who was being treated for stage IIIB melanoma and was receiving ipilimumab every 3 weeks as part of a clinical trial protocol. Thirty-six days after treatment with ipilimumab began, the patient complained of symmetrical painful paresthesias in the soles of his feet that rapidly progressed to his mid-calf. The patient experienced an inability to sense stimuli arising within the body regarding body position, motion, and equilibrium, which resulted in gait instability. The patient's ipilimumab was discontinued after 2 doses, and his symptoms did not

improve even with the addition of pregabalin 75 mg twice daily and a trial of prednisone 120 mg daily. The patient was then hospitalized for distal lower extremity weakness and a bilateral foot drop.

A brain and spine MRI was conducted and was found to be normal. Viral and bacterial etiologies were investigated and not found to be contributory. A lumbar puncture revealed red blood cell (RBC) cerebral spinal fluid (CSF) 1/mm³ (normal CSF value, negative), white blood cell (WBC) CSF 78/mm³ (normal CSF value, < 5/mm³), CSF protein 68 mg/dL (normal CSF value, 21-38 mg/dL), and CSF glucose 77 mg/dL (normal CSF value, 50-75 mg/dL). A nerve conduction study was conducted on day 55 and revealed

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symmetric sensorimotor polyneuropathy. The patient received a trial of methylprednisolone 1,000 mg daily for 5 days, and he experienced improvement in his sensory symptoms. He also received one dose of infliximab 440 mg for the treatment of his polyneuropathy, however he did not experience improvement in his symptom.

Ninety-one days after the start of his polyneuropathy, the patient was admitted to the hospital for fever, truncal rash, and worsening weakness and paresthesias. The patient exhibited significant proximal muscle weakness and a more severe distal muscle weakness with minimal movement in both hands and no movement below the ankles. The patient received a 5-day course of intravenous immunoglobulin, which did not produce symptomatic improvement. A repeat nerve conduction study showed worsening conduction that had progressed to severe sensorimotor polyneuropathy with demyelinating features. A repeat lumbar puncture revealed a continued elevation of CSF WBCs and CSF protein. The patient was then started on tacrolimus 0.3 mg/kg/day adjusted for optimal blood levels and methylprednisolone 250 mg every 6 hours for 10 days. A repeat lumbar puncture revealed no CSF RBC, WBC CSF 8/mm³, normal CSF protein, and CSF glucose of 133 mg/dL. The patient's symptoms stabilized. After physical rehabilitation, he was able to walk with the aid of a walker. However 3 years later, he still has a bilateral foot drop, walks with a cane, and has not been able to return to full-time work.

Case 2 occurred in a 62-year-old male with stage IIIA melanoma who had received interferon therapy for 2 months but could not tolerate it due to adverse effects. The patient was well controlled until he developed lung metastasis 7 years later. He received 2 cycles of interleukin 2 and temozolomide and then ipilimumab every 3 weeks for a total of 4 doses as part of a clinical trial protocol. The patient experienced an excellent response to therapy, however 1 month later he developed painful paresthesias and decreased proprioception below the ankles with preserved strength and reflexes. The patient experienced minor improvement with the addition of gabapentin 300 mg 3 times daily.

The patient had received one dose of ipilimumab during his maintenance phase; 1 month later he developed a fever with jaundice. His liver function tests were abnormal with elevated total bilirubin and transaminases. A liver biopsy revealed that he had hepatocellular damage with diffuse histolytic and lymphocytic infiltration. The patient was thought

to have drug-related autoimmune hepatitis, and his ipilimumab was stopped. He was treated with methylprednisolone and mycophenolate; he had a normalization of his liver function tests after 4 months. The patient's paresthesias completely resolved within a few months, and he remained disease-free 2 years after ipilimumab therapy.

The authors point out that the mechanism of action of ipilimumab involves the inhibition of cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). Activation of inflammatory cells in the peripheral nervous system and of glial cells in the spinal cord with production of inflammatory cytokines may have contributed to pain hypersensitivity. Neither of these patients had received significant treatment with neurotoxic chemotherapy. The first patient represented the severe end of the spectrum of immune-mediated neuropathy; his symptoms were biphasic and he did not respond to infliximab, high-dose corticosteroids or intravenous immunoglobulin. The second patient experienced the milder form of the disease with only sensory involvement, which responded to discontinuation of ipilimumab.

Thaipisuttikul I, Chapman P, Avila EK. Peripheral neuropathy associated with ipilimumab: A report of 2 cases. *J Immunother*. 2015;38(2):77-79.

IBUPROFEN-INDUCED ALLERGIC-TYPE LIVER INJURY

A 36-year-old female had been taking over-the-counter medication containing ibuprofen for the treatment of occasional intermittent headaches. Her headaches had increased recently, and she was taking her ibuprofen 4 times daily for the previous 20 days. She stopped taking ibuprofen because of gastrointestinal side effects. Five days after she had stopped her ibuprofen, she presented at a local hospital with a fever, skin rash, and brown urine. She was admitted to the hospital with a temperature of 39°C (102.2°F) and redness on her upper and lower limbs and face, which spread over a large area. Her admission lab values were aspartate aminotransferase (AST) 1,492 U/L (normal value, <35 U/L), alanine aminotransferase (ALT) 1,860 U/L (normal value, 10-35 U/L), alkaline phosphatase (ALP) 323 U/L (normal value, 44-147 U/L), total bilirubin 15.3 mg/dL (normal value, 0.3-1 mg/dL), direct bilirubin 10.4 mg/dL (normal value, 0.1-0.3 mg/dL), international normalized ratio (INR) of 1.76 (normal value, 0.9-1.2), and an elevated IgE of 11,900 IU/mL. The patient was also tested for hepatitis B and C, antinuclear antibodies, and human herpes virus-6, which were all negative.

A drug lymphocyte stimulation test was performed to identify drugs or components of drugs that may have caused the patient's allergic response. The only drug to test positive in the drug lymphocyte stimulation test was ibuprofen. A liver biopsy was performed 14 days after ibuprofen was discontinued, and the results supported the diagnosis of drug-induced liver injury. The patient's skin lesions were diagnosed as multiform exudative erythema, which supported a definitive diagnosis of allergic-type drug-induced liver disease caused by ibuprofen and complicated by systemic hypersensitivity and multiform exudative erythema. The patient was given methylprednisolone 1,000 mg intravenously daily for 3 days followed by a tapered course of oral corticosteroid. The patient's rash resolved, and her liver function tests returned to normal over the subsequent 4 weeks.

The authors stated, "Drug-induced systemic hypersensitivity reactions involve the development of a rash in response to the consumption of a drug accompanied by the dysfunction of any internal organ." Because ibuprofen is so commonly used by patients, it is important to identify other nonsteroidal anti-inflammatory drugs (NSAIDs) that have the potential to cause liver injury. The authors feel that the drug lymphocyte stimulation test is a useful tool for identifying offending drugs that cause drug-induced liver disease, particularly in allergic-type drug-induced liver disease.

The authors tested a number of NSAIDs utilizing the drug lymphocyte stimulation test, and several of these drugs tested positive for increased risk of causing allergic-type drug-induced liver disease. The following NSAIDs tested positive: naproxen, diclofenac, aspirin, celecoxib, and indomethacin. Two NSAIDs tested negatively: flurbiprofen and mefenamic acid. The authors "strongly suggest that the use of drugs containing agents testing positive on the drug lymphocyte stimulation test should be avoided in the future for this patient."

Watanabe T, Abe M, Tada F, et al. Drug-induced liver injury with serious multiform exudative erythema following the use of an over-the-counter medication containing ibuprofen. *Intern Med.* 2015;54:395-399.

TRIMETHOPRIM-SULFAMETHOXAZOLE-INDUCED IMMUNE THROMBOCYTOPENIA IN CHILDREN

The authors report 3 cases of drug-induced thrombocytopenia due to trimethoprim-sulfamethoxazole in children. The first case occurred in a 15-year-old female who had a platelet count of $5 \times 10^9/L$ (normal

range, $150\text{--}400 \times 10^9/L$) with a 2-day history of petechiae and bleeding gums. The patient had been treated 2 weeks earlier for pharyngitis with trimethoprim-sulfamethoxazole. The second case occurred in a 7-year-old female who had petechiae, ecchymosis, and mucosal hemorrhage with a platelet count of $6 \times 10^9/L$. She had been treated with trimethoprim-sulfamethoxazole for a urinary tract infection (UTI) 2 weeks earlier. The third case occurred in a 10-month-old male who had been started on trimethoprim-sulfamethoxazole prophylaxis for UTIs 3 weeks earlier. The child had petechiae and ecchymosis and a platelet count of $6 \times 10^9/L$. All 3 patients did not receive additional trimethoprim-sulfamethoxazole after presentation and were given 1 dose of intravenous immune globulin at a dose of 1 g/kg. All of the patients' platelet counts improved within several days, and normal platelet counts were sustained. All patients had detectable trimethoprim-sulfamethoxazole antibodies.

The authors reported these 3 cases because the usage of trimethoprim-sulfamethoxazole in children has increased due to the increasing incidence of community-acquired methicillin-resistant *Staphylococcus aureus*. Their goal is to raise awareness of this serious adverse effect of trimethoprim-sulfamethoxazole-induced immune thrombocytopenia with use of this commonly prescribed antimicrobial.

Hayashi M, Veltri MA, Curtis BR, et al. Immune thrombocytopenia due to trimethoprim-sulfamethoxazole; under-recognized adverse drug reaction in children? *Pediatr Blood Cancer.* 2015;62:922-923.

MESNA-INDUCED FIXED DRUG ERUPTION

The authors report 3 cases of mesna-induced fixed drug eruptions. The 3 cases occurred in patients with multiple sclerosis who had been receiving monthly cyclophosphamide, mesna, and methylprednisolone. Two of the patients also received ondansetron for nausea. All of the patients reported the development of red plaques with a burning sensation on their face. The first case occurred in a 53-year-old female who received treatment for 9 months and developed a drug eruption 48 hours after administration of mesna. The second patient was a 45-year-old male who had received mesna for 24 months and developed a drug eruption 24 hours after administration. The third case occurred in a 40-year-old female who had been receiving mesna for 20 months and developed a drug eruption 24 hours after mesna administration.

All 3 patients recovered from their drug eruption within a few days, with 1 patient having residual pigmentation of the skin in the affected area. Subsequent administration of the treatment triggered recurrence of the subcutaneous lesions at identical and new sites less than 12 hours after administration in patients 1 and 3 and 6 hours after administration in patient 2. Patient 2 experienced 2 recurrences of lesions with repeated mesna administration.

All 3 patients were skin patch-tested for mesna, methylprednisolone, and cyclophosphamide, and 2 of the patients were tested for ondansetron. The patch tests for mesna were positive for all 3 of the patients at days 2 and 4. None of the other tested medications tested positive in the patch test. All 3 patients continued to receive cyclophosphamide, methylprednisolone, and ondansetron and have not had a recurrence of their fixed drug eruption.

The authors explain that patients treated for autoimmune disorders with cyclophosphamide and mesna seem to be associated with a higher frequency of adverse skin reactions, which occurs up to a rate of 50%. The authors mention that mesna-induced fixed drug eruptions are uncommon, but health care professionals must be aware that hypersensitivity reactions of this type are possible with mesna.

Soria A, Lebrun-Vignes B, LeForestier N, et al. Fixed drug eruption due to mesna. *J Invest Allergol Clin Immunol*. 2015;25(6):444-445.

DIGOXIN-INDUCED OCULAR TOXICITY

A 91-year-old female presented to the emergency department complaining of dysphagia, vomiting, and blurry vision. The patient reported she felt so ill she felt she had to enter a nursing home. Her heart rate was 60 bpm, and her physical exam was unremarkable. The patient weighed 56 kg and was 5 ft tall; her calculated creatinine clearance was 18 mL/min. She lived alone and reported that her medical history included hypertension, hypercholesterolemia, type 2 diabetes, ischemic heart disease with heart failure, chronic kidney disease, gout, and breast cancer. Two years earlier, she had a pacemaker implanted for management of her atrial fibrillation. Her medication history included acenocoumarol (a warfarin derivative not available in the United States) titrated to an INR of 2-3, metoprolol, lisinopril, torsemide, simvastatin, anastrozole, ibandronate, lorazepam, folic acid, calcium, cholecalciferol, and zolpidem. One month prior to her visit to the emergency department, the patient was initiated on digoxin 0.25 mg daily and

diltiazem 90 mg daily. The cardiologist who had initiated digoxin therapy sent a letter to her general practitioner that her digoxin levels would need to be monitored and dosing adjusted accordingly.

In reviewing the patient's symptoms over the past month, it was found that the patient had a fall on the seventh day after starting digoxin and diltiazem and her general practitioner discontinued her diltiazem at this time while continuing digoxin at the 0.25 mg daily dose. On day 13 of digoxin therapy, the patient reported digestive systems and difficulty eating. From day 18 on, the patient complained of significant loss of vision in both eyes and she noted that everything looked white. It should be noted that the patient had a 10/10 visual acuity in both eyes documented 5 months prior to digoxin initiation. On day 21 of digoxin therapy, the patient had an emergency eye consultation and her visual acuity was 4/10 in the right eye and 5/10 in the left eye. At this time, the patient had lost 5 kg because of her persistent nausea and vomiting and her vision remained severely impaired.

The patient's symptoms varied from day to day and included blurry vision to the point she could not read printed text and snowy vision in which everything was bathed in white light. She reported a tendency to collide with objects on her right side, and she also reported seeing blue or purple spots when she closed her eyes and vivid colors appeared to be faded. She also experienced visual hallucinations of little human figures that did not frighten her who either appeared shortly before she fell asleep or upon awakening. Finally she also reported that she felt like she was on a rocking boat when lying in bed.

In the emergency department, her digoxin level was documented to be 5.7 ng/mL (normal range, 0.8-2 ng/mL). The patient's digoxin was stopped and her level decreased to 4 ng/mL on day 3 of her hospital stay and 1.1 ng/mL on day 10. Her digoxin half-life was calculated to be approximately 80 to 90 hours. Brain CT and gastrointestinal studies were conducted, and no findings were contributory to the patient's symptoms. The patient's nausea and vomiting dissipated over the next few days after digoxin was discontinued. She reported her general condition improved, and she began to gain weight.

On day 17 of her hospital stay, her visual symptoms were persistent, including snowy and blurry vision and peripheral fixed presence of perceived flashes of light; her ability to perceive colors was not fully normal. Her visual hallucinations continued

when she fell asleep, and her visual acuity was still decreased at 4/10 in the right eye and 5/10 in the left eye. She also reported red-green color blindness. The patient was discharged from the hospital after 44 days. She was still living at home 6 months after discharge. She reported subtle improvement of her visual acuity to 6/10 in the right eye and 5/10 in the left eye, however her red-green color blindness persisted.

The authors discuss the key factors that contributed to this patient's constellation of adverse events to digoxin. Since digoxin is a narrow therapeutic index medication, it is important to monitor and follow-up patients who are initiated on digoxin, especially if they have decreased renal function and a number of

comorbid conditions. In light of this patient's elevated digoxin level, cardiac symptoms would be expected to be the first adverse effects experienced; the fact that she had an implanted pacemaker most likely concealed her cardiac symptoms. The authors also point out that the speculative mechanism by which digoxin causes ocular symptoms may be related to $\text{Na}^+ \text{K}^+ \text{ATPase}$ inhibition. The insufficient communication between health care providers lead to her significantly elevated digoxin level as well as her persistent visual complications.

Renard D, Rubli E, Voide N, et al. Spectrum of digoxin-induced ocular toxicity: A case report and literature review. *BMC Res Notes*. 2015;(8)368:1-8. doi: 10.1186/s13104-015-1367-6. ■