ISMP Adverse Drug Reactions

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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.

CONNECTIVE TISSUE DISEASE FOLLOWING HEPATITIS B VACCINATION

A 43-year-old woman who did not have a family or personal history of autoimmune disorders received the first and second doses of hepatitis B virus (HBV) vaccine 1 month apart. A few days after the third and last dose (6-month dose), the patient began to complain of paresthesias in the left arm and hand as well as arthralgias in the upper extremities. One month after the last dose of the HBV vaccine, the patient exhibited localized areas of scalp alopecia. Three months after the last dose of HBV vaccine, the patient experienced several episodes of arthritis localized to the hands with mild pitting edema of the fingers. At this time, the patient also experienced progressive asthenia and an itchy pretibial rash.

Laboratory testing revealed positive antinuclear antibodies (ANA) 1:1320, whereas anti-dsDNA,

ENA profile, anti-citrullin, antiphospholipid, and rheumatoid factor were all negative and a complete blood count and C-reactive protein were also within normal limits. Electromyography revealed a sensory-type peripheral neuropathy of the median nerve of the left arm. Based on these findings, a diagnosis of undifferentiated connective tissue disease (UCTD) related to HBV vaccination was made approximately 1 year after the initial injection of HBV vaccine. Prednisone 25 mg daily and hydroxychloroquine 200 mg daily were initiated, and the patient experienced a prompt remission of all neurological, dermatological, and rheumatologic symptoms. Two months after the initiation of therapy, the antinuclear antibody became negative and prednisone therapy was discontinued.

The authors point out that when the patient was diagnosed in 2012 with UCTD, the symptoms failed to satisfy the 1997 American College of Rheumatology

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(ACR) criteria for the diagnosis of systemic lupus erythematosus (SLE) at the time. If the authors had retrospectively reclassified the patient according to the recent revision of the ACR, then the postvaccination symptoms would fulfill the criteria required for the diagnosis of SLE. However, because no new SLE signs or symptoms appeared in the 18 months of follow-up, some uncertainty between the diagnoses of UCTD and SLE remain.

The authors state that several autoimmune diseases have been described following HBV vaccination, such as demyelinating syndromes including multiple sclerosis, rheumatoid arthritis, SLE, autoimmune glomerular nephritis, panarteritis nodosa, type I diabetes, Graves disease, lichen planus, and Guillain-Barré syndrome. Recently, a syndrome named ASIA (autoimmune syndrome induced by adjuvants) has been reported. The symptoms of this syndrome appear after exposure to silicone, tetramethylpentadecane, pristaine, aluminum, and other adjuvants. The classification criteria of the syndrome include exposure to external stimuli (vaccines, silicone adjuvant) and the subsequent onset of clinical manifestations (myalgias, arthralgias, chronic fatigue, neurological manifestations, cognitive deficits fever, and dry mouth). The patient presented appears to be within the ASIA classification criteria. The authors note that HBV vaccine contains aluminum adjuvant and clinical symptoms appeared approximately 1 month after the first dose of HBV vaccine.

Bruzzese V, Zullo A, Hassan C. Connective tissue disease following hepatitis B vaccination. *J Clin Rheumatol*. 2013;19(5):280-281.

TOPIRAMATE-ASSOCIATED FATAL HEAT STROKE

A 40-year-old male was found at home by his father; he was unresponsive and “very hot to the touch” some 40 minutes before being evaluated by emergency medical services (EMS). His past medical history included a seizure disorder secondary to a prior gunshot wound to the head and diabetes for which he was taking topiramate, divalproex sodium, and rosiglitazone/metformin. No seizure activity was reported to or witnessed by EMS. The patient’s capillary glucose at the scene was 122 mg/dL. EMS administered oxygen, a 500 mL bolus of normal saline solution, and naloxone 4 mg IV with no discernible improvement in his condition. Upon arrival to the emergency department, the patient was unresponsive (Glasgow Come Scale score of 3), with decreased air movement bilaterally and regular heart rhythm. The patient’s vital signs included a heart rate of 60 beats per minute (bpm), blood pressure of 94/50 mm Hg,

respiratory rate of 32 breaths per minute, and a rectal temperature of 42.2°C (108°F), which later peaked at 43.2°C (109.8°F). The patient’s skin was hot and dry without rash. The patient then received lorazepam 4 mg IV and fosphenytoin 1 g IV, was placed on a cooling blanket, and was subsequently intubated. Additional IV lorazepam doses of 4 mg and 2 mg were administered with no response. Administration of dantrolene was considered but not initiated. The patient had a Foley catheter placed but no urine was produced, so additional boluses of normal saline were administered and cold compresses were placed on the patient’s body. Shortly after arrival, the patient’s blood pressure dropped to 78/36 mm Hg, and dopamine 10 µg/kg/min was administered via central line. The patient’s heart rate dropped; he went into cardiac arrest 54 minutes after he arrived at the emergency department. Arterial blood gasses that were drawn during cardiac arrest revealed a pH 7.12, pCO₂ 39.1 mm Hg, pO₂ 31.4 mm Hg, and a base excess of 16 mEq/L. Additional labs revealed a serum creatinine 3.7 mg/dL, serum lactate 4 mmol/L, serum creatinine kinase 6,101 IU/L, serum topiramate 8.8 µg/mL (therapeutic range, 2-12 µg/mL), and serum valproate 97 µg/mL (therapeutic range, 50-100 µg/mL). In spite of advanced cardiac life support and active cooling, the patient died 2 hours after arriving in the emergency department.

The US Food and Drug Administration (FDA) issued a warning in July 2003 following several case reports of topiramate-induced oligohydrosis. Oligohydrosis is defined as the deficient production and secretion of sweat. The FDA recommended close monitoring of patients receiving topiramate, especially children, for reduced sweating and increased body temperature, particularly in hot weather. Although cases of oligohydrosis have been reported, they have generally been mild and reversible with the decrease in dose or discontinuation of topiramate therapy. A study by Ziad et al found that 10.5% of all patients receiving topiramate in an epilepsy clinic in Beirut spontaneously reported hyperthermia when asked generically about adverse experiences, compared with 0.15% of patients taking other antiepileptic medications. Furthermore, temperatures between 39°C (102.2°F) and 39.5°C (103.1°F) were reported in 15.4% of those taking topiramate and reporting hyperthermia. As in previous reports, the higher body temperatures typically occurred in warm months (May to October). The current case occurred in July; the peak temperature on the day of the event was 33.9°C (93°F).

The authors ruled out valproate as a possible cause of the patient's hyperthermia due to the fact that in prior published cases of sodium valproate hypersensitivity, skin lesions have been a common finding. Furthermore, valproate hypersensitivity generally occurs in patients within 8 weeks of initiating the drug. The current patient had been receiving valproate for several months. The possible mechanism of topiramate-induced sweat suppression and fever is based in the fact that topiramate inhibits carbonic anhydrase isoenzymes II and IV, preferentially. These isoenzymes are found in human eccrine sweat glands.

Because of the growing list of indications and widespread usage of topiramate, the authors warn that health care providers should be aware of the risk of oligohidrosis and hyperthermia, particularly in warm climates.

Borron SW, Woolard R, Watts S. Fatal heat stroke associated with topiramate therapy. *Am J Emerg Med.* 2013;31:1720.e5-1720.e6.

Zaid el K, Rahi AC, Hamdan SA, et al. Age dose and environmental temperature are risk factors for topiramate-related hyperthermia. *Neurology.* 2005;65:1139-1140.

RAMELTEON-INDUCED AUTOIMMUNE HEPATITIS

A 50-year-old male with a history of depression and chronic alcohol consumption developed worsening hepatitis after starting ramelteon (*Rozerem*) 8 mg daily at bedtime. Routine liver function tests before starting ramelteon were aspartate aminotransferase (AST) 57 IU/L (reference range, 15-41 IU/L), alanine aminotransferase (ALT) 63 IU/L (reference range, 17-63 IU/L), alkaline phosphatase (ALP) 105 IU/L (reference range, 32-91 IU/L), and albumin 4.5 g/dL (reference range, 3.5-4.8 g/dL). One month after initiation of ramelteon, liver function tests were repeated because of patient complaints of worsening fatigue. Total bilirubin was 1.6 mg/dL (reference range, 0.3-1.2 mg/dL), ALP 138 IU/L, AST 858 IU/L, ALT 718 IU/L, and albumin 4.5 g/dL (reference range, 3.5-4.8 g/dL). Shortly thereafter, the patient began to note jaundice of his skin and sclera, at which time all medications (ramelteon, alprazolam, and escitalopram) were discontinued. Three weeks after the discontinuation of all medications, laboratory results were total bilirubin 34.2 mg/dL, direct bilirubin 21.6 mg/dL (reference range, 0.1-0.5 mg/dL), ALP 273 IU/L, AST 340 IU/L, ALT 290 IU/L, albumin 2.3 g/dL, international normalized ratio (INR) 1.7, creatinine 2.3 mg/dL (reference

range, 0.6-1.3 mg/dL), and a leukocyte count of $13,700 \times 10^3/\mu\text{L}$ (reference range, 3.4 to $11.2 \times 10^3/\mu\text{L}$) without eosinophilia. These laboratory values yield a Model for End-Stage Liver Disease score of 22, which predicts a 3-month mortality of 19.6%. At this time, the patient was hospitalized for further workup and treatment.

During the prior weeks of worsening fatigue and abnormal liver function tests before admission, the patient denied changes in abdominal girth or cognition. The patient did admit to a recent increase in his chronic alcohol consumption to more than 6 drinks per day. The patient denied any personal or family history of autoimmune diseases. The only new medication or exposure noted by the patient at the time of admission was ramelteon, which he started 7 weeks prior. The patient had been receiving his alprazolam and escitalopram for more than 2 years without a change in dose. On physical examination, the patient had significant scleral icterus, mild hepatomegaly, and a distended but soft abdomen with a fluid wave. The results of serologic tests for hepatitis A, B, C, and E viruses were negative. Antinuclear antibody titer was not obtained, however an IgA level was 749 mg/dL (reference range, 70-312 mg/dL), IgG level was 1,710 mg/dL (reference range, 639-1,349 mg/dL), and IgM level of 104 mg/dL (reference range, 56-352 mg/dL).

An ultrasound was performed and revealed hepatosplenomegaly, liver nodularity compatible with cirrhosis, and large volume abdominopelvic ascites. The patient underwent diagnostic paracentesis and a subsequent transjugular liver biopsy, which showed fulminant hepatitis with confluent necrosis, significant parenchymal loss, and lymphoplasmacytic infiltrate and rosette formation consistent with autoimmune hepatitis (AIH). The patient was subsequently discharged on a course of oral prednisone 60 mg for the treatment of AIH.

Three weeks later, the patient was found to have mild improvement and he underwent a large volume paracentesis to manage his ascites. Laboratory studies of the fluid revealed a leukocyte count of $3,700/\mu\text{L}$ with 94% neutrophils, which is consistent with spontaneous bacterial peritonitis (SBP). The patient was urged to seek hospitalization but refused, and he was initiated on a course of outpatient oral antibiotics for his SBP. The following day, the patient experienced worsening abdominal pain and confusion that caused him to visit the local emergency department. He was found to have a temperature of 35.5°C (95.9°F), pulse of 103 bpm, blood pressure

of 104/81 mm Hg, and leukocyte count of 15,100/ μ L with 93% neutrophils. The patient was started on intravenous antibiotics and albumin, however he rapidly worsened and required intubation for respiratory failure. He was transferred to the intensive care unit. The patient's family opted for comfort care measures, and the patient expired several hours later. Autopsy indicated that the cause of death was systemic inflammatory response syndrome secondary to SBP, with the underlying cause of death noted to be AIH.

The authors suggest that ramelteon had a role in the etiology of the patient's disease, considering the temporal relationship between ramelteon and the development of AIH and the immunostimulatory properties that have been elucidated for melatonergic agents. Ramelteon functions as a melatonin agonist with a high affinity for membrane receptors MT1 and MT2. Melatonin is secreted by the pineal gland in a circadian manner and serves as a biological signal of darkness. As its duration of release is proportional to night length, this hormone informs multiple organ systems about time of day and season. Melatonin is generally regarded as immunostimulatory, and some evidence suggests it may play a role in autoimmune diseases. On the basis of melatonin's role in the immune system, there is some concern that this drug may exacerbate autoimmune diseases. The European Medicines Agency, in particular, advises against the use of melatonin in patients with such conditions. There is a growing body of evidence for melatonin's disease-promoting effects in rheumatoid arthritis. Rheumatoid arthritis is an autoimmune process that is driven by T cells and is associated with the production of autoantibodies. In addition to being immunostimulatory, melatonin has certain effects that may promote autoimmunity. In particular, this substance has been shown to reduce activation-induced cell death and the apoptotic process that occurs in T cells after restimulation through antigen receptor complexes. Ramelteon is distinct pharmacologically from melatonin in several important ways. To produce hypnotic effects, both agents bind to membrane receptors MT1 and MT2, although ramelteon does so with higher affinity. Ramelteon has a longer half-life than melatonin ($t_{1/2}$ = 1-2 hours and < 30 minutes, respectively), as well as a unique metabolite (M-II) that substantially contributes to its pharmacological activity. M-II is longer lasting and can attain concentrations 20- to 100-fold higher than ramelteon.

The authors recommend that, as stimulators of the immune system, melatonergic agents may potentiate autoimmunity. Although further research is needed, ramelteon should be used with caution, especially in patients at risk for autoimmune disease, given its pleiotropic effects.

Fourman LT, Meyer BR. Autoimmune hepatitis in association with ramelteon. *J Clin Gastroenterol*. 2013;47(7):651-654.

ACUTE OXALIPLATIN-INDUCED THROMBOTIC THROMBOCYTOPENIC PURPURA

A 68-year-old female with liver and peritoneal metastases from colon cancer experienced a sudden drop in platelet count. The patient received an adjuvant chemotherapy regimen (FOLFOX) with infusional fluorouracil, leucovorin, and oxaliplatin (*Eloxatin*) in 2006 with no adverse effects. In 2011, after evidence of relapsing disease, additional cycles of chemotherapy with FOLFOX were administered. The first 2 cycles were concluded with no adverse effects, and routine blood tests were normal (platelet count $194 \times 10^3/\mu$ L; INR 1.06). However 30 minutes after the third oxaliplatin infusion, the patient experienced severe bleeding of the gums and nail beds, epistaxis, and hematuria. Vital signs were normal at this time. Blood tests were repeated, with evidence of severe thrombocytopenia (platelets, $5 \times 10^3/\mu$ L) and increased INR of 1.77. Although a more complete coagulation assay including fibrinogen, antithrombin, and D-dimer parameters was requested, the blood sample could not be processed because of rapid blood clotting in the test tube. Therefore, a platelet transfusion was given, which immediately resolved the clinical problem. A new blood sample that was taken 18 hours later, which showed an increase in the platelet count ($33 \times 10^3/\mu$ L) and a decrease in INR to 1.32. Blood parameters had normalized by the next day.

The authors theorize that in this patient oxaliplatin induced the fibrinogen receptor exposure independently of the influence of the endothelium and that the observed thrombocytopenia may have been caused by an oxaliplatin-mediated autoimmune response. Other authors have theorized that serum antioxaliplatin immunoglobulin G could represent the initial stimulus that is needed for sudden platelet activation. Such an observation is consistent with the fact that no cases of thrombotic thrombocytopenic purpura have ever been reported during

the first cycle of FOLFOX. The authors suggest that additional studies are needed to clarify whether an inexpensive method is needed to assess immunologic sensitization to oxaliplatin before its administration, so that the dramatic clinical impact of induced thrombotic thrombocytopenic purpura can be avoided.

Lucchesi A, Carloni S, Cangini D, et al. Acute oxaliplatin-induced thrombotic thrombocytopenic purpura: A case report and results from a cytofluorimetric assay of platelet fibrinogen receptor. *J Clin Oncol*. 2013;31(16):2061-2062.

Niu J, Mims MP. Oxaliplatin-induced thrombotic thrombocytopenic purpura: Case report and literature review. *J Clin Oncol*. 2012;30:e312-e314. ■