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.

CHRONIC MARIJUANA USE ASSOCIATED WITH RECURRENT DIABETIC KETOACIDOSIS

Two case reports of recurrent diabetic ketoacidosis (DKA) that occurred subsequent to chronic marijuana usage were reported in the literature by Gallo and Shah. The first case occurred in a 33-year-old male who had type I diabetes for the preceding 15 years. During the prior 24 months, the patient had been admitted to the hospital and treated for DKA 7 times. The patient reported that all his DKA episodes started with an abrupt onset of nausea, vomiting, and abdominal pain that progressively worsened, leading to dehydration and ketosis. The patient denied missing insulin injections, and his A1C was in the range

of 7.5% to 8%. All standard laboratory tests were inconclusive, however his medical history noted that he was treated for gastroparesis and cyclic vomiting syndrome. Past admission records revealed that the patient had tested positive for tetrahydrocannabinol (THC) on a urine drug screen. Upon questioning, the patient revealed he utilized marijuana either by smoking or by eating potent edible forms for the past 10 years. The patient was suspected of having cannabinoid hyperemesis syndrome and was instructed to discontinue his marijuana usage. In the 8 months after stopping his marijuana usage, the patient did not have any bouts of nausea or vomiting and has not had a recurrence of DKA.

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The second case occurred in a 23-year-old female with type I diabetes for the previous 17 years. She had 4 episodes of DKA over a 3-month period. She reported nausea, vomiting, and abdominal pain prior to each of her DKA hospitalizations. As in the case of the previous patient, her laboratory tests were inconclusive and an abdominal ultrasound was also normal. Because her symptoms were similar to patient 1, she was asked about possible marijuana usage. She stated that she had been ingesting edible high-potency marijuana for 1 week to treat back pain. While her pain dissipated, she began suffering from intractable nausea and vomiting after 3 to 4 days of edible marijuana usage. Her gastrointestinal symptoms continued for 2 months after stopping her edible marijuana intake. Eventually the patient had a full recovery from her gastrointestinal symptoms and did not ingest edible marijuana. Over the next 3 months, she did not have a vomiting episode or a recurrence of DKA.

With the legalization of marijuana, these symptoms could manifest in diabetic patients. The authors (Ghosh et al and Monte et al) point out that while cannabinoids are being used for the treatment of nausea, there has been an increase in cyclic vomiting-like presentations among chronic recreational marijuana users in Colorado. The authors mention that the possible mechanism of cannabinoid hyperemesis syndrome may be a severely impaired gastric emptying; a diabetic patient may be at increased risk, because they may have concurrent diabetic gastroparesis of varying degrees. Typically cannabinoid hyperemesis syndrome occurs with long-term marijuana usage, however patient 2 only used an edible product for 1 week and the adverse gastrointestinal effects lasted for 2 months.

Because there is no specific regulation of THC content in various edible and smokable marijuana products, the authors posit that this may explain the variable effect seen in these 2 patients. Since THC is lipophilic, a high-potency THC product may have prolonged effects. The authors recommend that health professionals investigate marijuana usage in diabetic patients with severe gastroparesis, recurrent vomiting, or diabetic ketoacidosis.

Gallo T, Shah VN. An unusual cause of recurrent diabetic ketoacidosis in type 1 diabetics. *Am J Med.* 2016;129(8):e139-e140.

Ghosh TS, Van Dyke M, Maffey A, et al. Medical marijuana's public health lessons – implications for retail marijuana in Colorado. *N Engl J Med.* 2015;372(11):991-993.

Monte AA, Zane RD, Heard KJ. The implications of marijuana legalization in Colorado. *JAMA.* 2015;313(3):241-242.

LAMOTRIGINE-INDUCED CATAPLEXY

A 37-year-old female with bipolar disorder was treated with multiple medications. She had received olanzapine, clordiazepoxide, lithium carbonate, and risperidone at different times. She was stabilized on lithium 800 mg daily, which produced a serum lithium level of 0.7 mEq/L (therapeutic range, 0.5-1.5 mEq/L). The patient complained of insomnia and was prescribed lormetazepam 2 mg at bedtime. Lormetazepam is a short-acting benzodiazepine indicated for the short-term treatment of insomnia. The patient reported sadness, irritability, motiveless fear, and galactorrhea, and she developed acne. Her lithium was gradually withdrawn, and she was initiated on lamotrigine (*Lamictal*) 200 mg daily.

Approximately 1 month after the initiation of lamotrigine, the patient reported her mood symptoms had begun to improve, but she began to suffer from sudden episodes of weakness in her lower limbs that caused her to fall. She did not report any loss of consciousness when the weakness occurred. The episodes of weakness lasted 2 to 3 minutes. Quetiapine 100 mg daily at bedtime was added to her regimen for her persistent insomnia, although she stopped taking this medication on her own. Asenapine 5 mg daily was added to her regimen because she reported the sensation that she was being observed. Approximately 4 months later, the patient stopped taking asenapine and restarted quetiapine 100 mg at bedtime to treat her insomnia.

Two months later, the patient was evaluated for limb weakness and falling, which had been occurring at least once monthly. At this time, her drug regimen consisted of lamotrigine 200 mg daily, quetiapine 100 mg daily, asenapine 10 mg daily, and lormetazepam 2 mg daily. Her neurologic examination was normal as was a brain MRI and electroencephalogram. She was diagnosed at this time with cataplectic episodes, and her dosage of lamotrigine was decreased to 100 mg daily. The patient eventually increased her lamotrigine dosage to 200 mg daily due to increased nervousness. Asenapine and quetiapine were gradually withdrawn from her regimen.

Approximately 10 months later, the patient was initiated on valproate 500 mg daily and maintained on lamotrigine 200 mg daily. She reported that the episodes of limb weakness and falling had persisted throughout this time. Over the next 5 months, lamotrigine was gradually withdrawn, desvenlafaxine 50 mg daily was initiated, and her valproate dosage was increased to 700 mg daily. The patient did

not experience any further episodes of limb weakness or falling after lamotrigine withdrawal, which continued during 2 years of follow-up.

The authors note that the occurrence of cataplexy in patients without narcolepsy and cataplexy associated with drugs is very rare. They state, "The development of clinical cataplexy seems to be related to an increased inhibitory and reduced excitatory signalling in the brain, leading to a reduction in skeletal muscle neurons." The possible mechanism of induction of cataplexy by lamotrigine in this patient could be due to inhibition of glutamatergic and noradrenergic mechanisms together with an increase in GABAergic effects.

Alonso-Navarro H, Montes JM, Plaza-Nieto JF, et al. Cataplexy possibly associated with lamotrigine. *J Clin Psychopharmacol*. 2016;36(4):400-401.

TRIMETHOPRIM-SULFAMETHOXAZOLE-INDUCED HYPONATREMIA

An 82-year-old female presented to an emergency department and was admitted with altered mental status. She was treated empirically for complicated cystitis with fosfomycin 3 g orally. She was discharged with trimethoprim-sulfamethoxazole (TMP-SMZ) 160 mg/800 mg for an additional 7 days of therapy. On admission to the hospital, her chem-7, complete blood count (CBC), TSH, and hepatic panel were normal, except for a serum sodium of 132 mmol/L (normal range, 133-145 mmol/L). A serum sodium level obtained 1 month prior to her presentation was 134 mmol/L. The patient's medication history included acetaminophen, allopurinol, cholecalciferol, digoxin, docusate, famotidine, hydralazine, hydrocodone/acetaminophen, insulin glargine, lipase-protease-amylase capsules, lisinopril, methotrexate, metoprolol tartrate, oral multivitamin, nifedipine, prednisone, sotalol, warfarin, and a lutein capsule. All of her medications were unchanged during the prior month, except for a slight increase in her hydrocodone/acetaminophen dosage.

Eight days after her discharge, she visited her primary care physician complaining of depression and an inability to sleep, for which she was prescribed mirtazapine 7.5 mg at bedtime. Lab results from her office visit revealed a serum sodium of 121 mmol/L and an increased but normal serum potassium of 4.7 mmol/L. She was instructed to hold her lisinopril due to her increasing potassium and not to continue her mirtazapine. Admission to the hospital was encouraged, but the patient refused. She was instructed

to increase her salt and fluid intake. Two days later, her serum sodium had risen to 123 mmol/L, and it normalized over the next 8 days to 138 mmol/L. She reinitiated her mirtazapine and lisinopril without sodium or potassium alterations.

Several months later, she again was treated for a urinary tract infection with TMP-SMZ 160 mg/800 mg 2 tablets twice daily for 7 days. Three days after starting TMP-SMZ, she was admitted to the hospital for a potential transient ischemic attack. Her labs revealed serum sodium of 132 mmol/L, which decreased to 129 mmol/L the next day. Her urine cultures were negative, and TMP-SMZ was discontinued. The patient's hyponatremia was treated with normal saline boluses and a continuous infusion of 1,000 to 1,500 mL/day of normal saline.

The authors did an excellent job of reviewing the literature and investigating the occurrences of hyponatremia due to TMP-SMZ as well as a potential mechanism for this adverse effect. The authors state, "It has been hypothesized that TMP-SMZ blocks aldosterone-mediated sodium resorption in the collecting duct causing serum sodium concentrations to decline. Trimethoprim is also structurally related to potassium-sparing diuretics, which block sodium reabsorption at the distal nephron leading to potential hyponatremia and/or hyperkalemia." The authors cited a number of cases of TMP-SMZ-induced hyponatremia. They also scored the adverse event utilizing the Naranjo scale. The score was a 9, which indicated that TMP-SMZ was the likely cause of the patient's hyponatremia. They warn that for patients who may be prone to hyponatremia, alternate antimicrobial therapy should be selected if possible. If TMP-SMZ must be utilized, then the patients should have their electrolytes monitored prior to the initiation of TMP-SMZ and throughout therapy. Patients at risk of TMP-SMZ-induced hyponatremia include the elderly or those with underlying kidney dysfunction.

Huntsberry AM, Linnebur SA, Vejar M. Hyponatremia after initiation and rechallenge with trimethoprim-sulfamethoxazole in an older adult. *Clin Interv Aging*. 2015;10:1091-1096.

ZIPRASIDONE-INDUCED SLEEPWALKING AND SLEEP-RELATED EATING

A 28-year-old male with schizoaffective disorder was receiving varying dosages of ziprasidone (*Geodon*) to control his symptoms. He had been receiving 40 mg twice daily for 9.5 months and was still experiencing symptoms; his dosage was increased

to 60 mg twice daily. A month after the dosage change, the patient reported disabling daytime sedation; his ziprasidone dosage was adjusted to 40 mg in the morning and 60 mg in the evening. Two months later, his evening dosage was increased to 80 mg because of recurrent symptoms. This new regimen of 40 mg in the morning and 80 mg in the evening seemed to control his symptoms without daytime sedation.

Three months after the final dosage increase, the patient reported episodes of sleepwalking and sleep-related eating during most nights. His girlfriend observed these behaviors, however the patient had no recollection of his behavior in the morning. He noted that this behavior began 6 months earlier when his ziprasidone dosage was increased to 60 mg twice daily. He had not displayed this activity when he was receiving 40 mg twice daily. His girlfriend reported that this behavior starts in the first half of the night and the patient has his eyes open while sleepwalking and sleep-related eating. She noted he ate applesauce, candies, cookies, and pasta. She even observed him cooking pasta in the middle of the night; he had no recollection of his activity in the morning. The patient did not have any history of sleepwalking or an eating disorder.

The patient's evening dosage of ziprasidone was discontinued while his morning dosage was maintained at 40 mg. In 2 weeks, the patient reported that his sleepwalking and sleep-related eating had ceased. However, he complained of insomnia since the evening ziprasidone was discontinued. The patient's evening ziprasidone dosage was reinitiated at 80 mg for 1 week. One week later, the patient reported that his sleepwalking and sleep-related eating had resumed. His evening ziprasidone dosage was discontinued and replaced with an evening dosage of quetiapine 100 mg while his ziprasidone 40 mg morning dosage was continued. Over the next 2 months, the patient did not experience episodes of sleepwalking or sleep-related eating.

Non-rapid eye movement sleep arousal disorders like sleepwalking are postulated to be induced by an increase in slow wave sleep. The author stated, "Atypical antipsychotics such as olanzapine and quetiapine have been implicated both to increase slow wave sleep and induction of partial arousals during slow wave sleep, along with motor disinhibition during slow wave sleep mediated via serotonin 5-HT_{2A/2C} receptor antagonism in the pathophysiology of sleepwalking." Additionally, "sleep-related eating in association with sleepwalking has been postulated to be related to 5-HT_{2C} antagonism resulting in increased

appetite via induction of leptin resistance at the level of the hypothalamus." The author concludes that "5-HT_{2A/2C} antagonism by ziprasidone was involved in the etiology of sleepwalking and sleep-related eating in this case," and "clinicians should be aware of this type of sleep dysfunction as a rare but possible adverse effect of atypical antipsychotic drug therapy."

Das P. A case of sleepwalking with sleep-related eating associated with ziprasidone therapy in a patient with schizoaffective disorder. *J Clin Psychopharmacol*. 2016;36(4):393-394.

METABOLIC ACIDOSIS ASSOCIATED WITH ACETAMINOPHEN

A 25-year-old Caucasian female was admitted to the hospital for *Staphylococcus aureus* endocarditis that was methicillin-sensitive; she was started on nafcillin. She had a history of intravenous drug abuse and was in severe pain from many septic emboli that was not well controlled by morphine. She was initiated on hydrocodone-acetaminophen with better pain management. Three weeks into her antibiotic treatment, she continued to have pain and intermittent fevers despite negative blood cultures. She then developed high anion gap acidosis, while she remained awake and oriented with no change in her vital signs. Significant lab results revealed a decreasing serum bicarbonate, which reached a low of 16 mEq/L (normal range, 22-26 mEq/L). Her chloride was 107 mEq/L (normal range, 95-107 mEq/L), her sodium was 139 mEq/L (normal range, 135-147 mEq/L), and her calculated anion gap was 16 mEq/L (normal range, 8-16 mEq/L). Her venous blood gas had a pH of 7.42 (normal range, 7.32-7.43) and pCO₂ 22 mm Hg (normal range, 40-60 mm Hg). Her liver and renal function tests were normal.

The patient had received approximately 2.5 g of acetaminophen daily for control of her pain and fever. All forms of acetaminophen were discontinued, and she was initiated on fentanyl for pain management. Her anion gap acidosis resolved after acetaminophen discontinuation. Her urine was sent for organic acid analysis, and the analysis revealed a large elevation of 5-oxyproline. This confirmed the diagnosis of 5-oxyproline anion gap acidosis.

The authors stated, "Acetaminophen is metabolized into acetaminophen cysteine and also hydroxylated into n-acetyl-p-benzoquinone imine, a highly reactive oxidizing agent that is conjugated and reduced by glutathione. Chronic acetaminophen use reduces both cysteine and glutathione levels. Cyste-

ine is required in the production of glutathione, and in the depletion of both, a 5-oxoproline intermediate is produced. This 5-oxoproline cycle depletes adenosine triphosphate, and over time, results in an accumulation of 5-oxoproline and the subsequent anion gap acidosis.” It should be noted that acetaminophen levels are not usually in the toxic

range when this occurs and patients can manifest as asymptomatic acidosis to coma. Discontinuation of acetaminophen and hydration will usually resolve the acidosis and in severe cases N-acetylcysteine has been administered.

Kamran H, Ram N. Chronic acetaminophen use associated with anion-gap metabolic acidosis. *Am J Med.* 2016;129(8):e127-e128. ■