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ISMP Adverse Drug Reactions

Garcinia Cambogia–Induced Acute Hepatitis

Varenicline-Induced Parkinsonism

Resistant Hypocalcemia After Zoledronic Acid Administration

Zonisamide-Induced Acute Kidney Injury

Psychosis Associated with Guanfacine

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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.

GARCINIA CAMBOGIA–INDUCED ACUTE HEPATITIS

A 42-year-old female presented to an emergency department complaining of acute onset of abdominal pain in her right upper quadrant. She rated the pain as 10 out of 10 in intensity and sharpness, and it radiated to her right shoulder. The patient also complained of nausea with no reported emesis. The patient's medical history included hypertension, chronic kidney disease stage 5, type 2 diabetes, chronic back pain, hemochromatosis, and obesity. Her medication history included hydralazine and hydrocodone/acetaminophen 7.5 mg/325 mg every 4 to 6 hours for increased back pain over the previous 3 days. The patient denied the use of alcohol.

On examination, the patient's vital signs were unremarkable, however laboratory analysis revealed the following abnormalities: alanine aminotransferase (ALT) 1277 µ/L (normal value, 7-45 µ/L), aspartate aminotransferase (AST) 2792 µ/L (normal value, 8-43 µ/L), alkaline phosphatase 283 µ/L (normal value, 37-98 µ/L), and ferritin 12,198 mcg/L (normal value, 11-307 mcg/L). Further testing revealed the following negative results: viral hepatitis panel, antinuclear antibody, antihistone antibody, antimitochondrial antibody, and a negative blood alcohol level. Her acetaminophen level was within the normal range. An abdominal ultrasound did not reveal any significant findings. Upon further questioning,

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patient disclosed that a week earlier she had started taking pure Garcinia cambogia for weight loss. Further use of the Garcinia cambogia supplement was stopped, and she was given N-acetylcysteine as a precaution against possible acetaminophen toxicity, although she did not exceed her prescribed dosage of hydrocodone/acetaminophen and her acetaminophen level was within the normal range.

Follow-up laboratory results on day 2 revealed that the patient's ALT had risen to a maximum of 1939 μ/L while her AST had risen to a maximum of 3165 μ/L with an increased international normalized range (INR) of 1.3 (normal value, 0.8-1.1). The patient then received several days of supportive care, and her abdominal pain resolved and her liver enzymes returned to baseline values. The patient was eventually discharged on hospital day 4 and received close outpatient follow-up with a hepatologist. Over the next 4 months, the patient's symptoms did not recur and continued normalization of her liver function studies was noted. In light of the patient's presentation with elevated liver enzymes in the setting of a baseline liver inflammation in combination with the use of acetaminophen and the introduction of the hepatotoxic herbal supplement, the diagnosis of acute hepatitis secondary to Garcinia cambogia is very likely.

The authors point out that Garcinia cambogia is a fruit found in Africa and Asia and is commonly advertised as an antiobesity herbal supplement. The active component of Garcinia cambogia is hydroxycitric acid, and it has been implicated in cases of hepatotoxicity by its association with the product *Hydroxycut*. The authors warn, "The general public's easy access to these supplements is of great concern, especially considering the Food and Drug Administration does not review them for efficacy and safety." The authors suggest that health care professionals need to be aware of the potential hepatotoxic effects of herbal supplements and patients should routinely be asked about their use of these products.

Melendez-Rosado J, Snipelisky D, Matcha G, et al. Acute hepatitis induced by pure Garcinia cambogia. *J Clin Gastroenterol*. 2015;49(5):449-450.

VARENICLINE-INDUCED PARKINSONISM

A 35-year-old male was admitted to the neurology service of a university hospital with symptoms of tremor, rigidity, speech disturbance, and slowing down of movements. The patient did not have a history of any recent infection, trauma, psychiatric disorder, or medical illness. He reported only receiving varenicline (*Chantix*); he had not taken an antiemetic, antipsychotic, antidepressant, or any other medication including alcohol or illicit drugs. The patient had started varenicline 15 days earlier. He began his varenicline dosage regimen with 0.5 mg daily and increased his dosage to 1 mg daily after the fifth day. The patient noted that his movement symptoms began 10 days after the onset of treatment.

The patient's vital signs were noted to be within normal limits, however his physical and neurological exam revealed a bilateral resting tremor and mildly suppressed movements in his upper extremities. The patient also exhibited cogwheel rigidity in all of his extremities together with bradykinesia, mask-like facial expression, dysarthria, and shortened steps while walking. The patient's complete blood count (CBC), chem-7, liver function tests, renal function tests, and urinalysis were all within normal limits. An MRI was taken of the patient's brain, and there were no pathological findings; the ECG findings were unremarkable.

Based on the patient's presentation and the additional findings, the patient was diagnosed with drug-related Parkinsonism. It was suggested to the patient that his dosage of varenicline be decreased in a stepwise fashion to verify that this reaction was dose dependent. The patient rejected this suggestion and expressed his discomfort with the condition; he voluntarily stopped using varenicline and refused the treatment of his Parkinsonism with biperiden. During the 2 weeks after the patient stopped taking his varenicline, he reported that his Parkinsonism symptoms were alleviated. The patient was seen by the treating physicians 4 weeks after stopping his varenicline, and all of his Parkinsonism symptoms were completely resolved. The patient also reported that he had not resumed smoking and had not started any other smoking cessation medications. The patient was lost to follow-up after this visit.

Varenicline has been associated with adverse effects such as agitation, aggression, suicidal tendencies, and changes in mood. Recent reports have detailed varenicline exacerbating the symptoms of schizophrenia, inducing manic episodes in bipolar patients, mixed mood, and psychotic episodes in patients with a history of depression. However Parkinson-type adverse effects are not expected nor have they been reported with the use of varenicline. Parkinsonism is observed with dopamine receptor antagonists, and the authors report that it is difficult to hypothesize any precise mechanism between varenicline and Parkinsonism.

The authors emphasize that since varenicline acts as a partial agonist/antagonist for the $\alpha_4\beta_2$ nicotinic acetylcholine receptor; varenicline's partial agonist activity induces a modest receptor stimulation that attenuates the symptoms of nicotine withdrawal. However the authors point out that varenicline also inhibits the surge of dopamine release believed to be responsible for the reinforcement and reward associated with tobacco use by preventing nicotine from activation of $\alpha_4\beta_2$ nicotinic acetylcholine receptors. As a result of this, the dopaminergic mesolimbic system cannot be activated. The authors state, "We think that Parkinsonism may be related to the relative dopaminergic deficiency caused by the use of varenicline in comparison with the use of tobacco." The authors warn that varenicline can lead to extrapyramidal side effects in some patients and the benefits and risk of any side effect should be taken into consideration before initiating varenicline.

Uca AU, Kozak HH, Uguz F, et al. Parkinsonism related to varenicline in a patient during smoking cessation. *J Clin Psychopharmacol.* 2015;35(3):355-356.

RESISTANT HYPOCALCEMIA AFTER ZOLEDRONIC ACID ADMINISTRATION

A 73-year-old African American female who had been recently diagnosed with immunoglobulin G multiple myeloma presented to the emergency department with a 2-day history of fever (102.8°F [39.3°C]), nausea, vomiting, and dizziness and she was obtunded. Her initial laboratory results revealed pancytopenia, elevated creatinine, and a corrected calcium of 7.3 mg/dL (normal value, 8.5-10.2 mg/dL) while her other electrolytes were within normal limits. Ten days prior to her presentation, she had received a single dose of zoledronic acid (*Reclast*, *Zometa*), 3 doses of bortezomib, and 7 doses of lenalidomide in addition to weekly dexamethasone. Based on her presentation and objective findings, she was diagnosed with neutropenic fever, acute renal failure, and severe hypocalcemia. The patient was initiated on vancomycin and cefepime, and she was given calcium gluconate boluses for her hypocalcemia.

After 24 hours of treatment, the patient's mental status did not improve, she remained febrile, and her kidney function worsened. The patient's calcium level became undetectable (<5 mg/dL) and her ionized calcium was 0.66 mmol/L (normal value, 1.1-1.3 mmol/L). The patient was then started on a calcium gluconate infusion in addition to the calcium gluconate boluses. The calcium infusion and boluses did not increase her calcium level. The patient's vitamin D level was measured and found to be low at 13 ng/dL (normal value, 8-80 ng/dL). This vitamin D level was measured on a day when the patient's serum creatinine was measured at 8 mg/dL. The patient was started on paricalcitol, and her calcium level improved to 8.4 mg/dL but did not revert to normal. In spite of aggressive calcium replacement, the patient remained persistently hypocalcemic and eventually developed tonic-clonic seizures. Her EKG also revealed a QT interval of 500 ms. Subsequent neuroimaging was normal except for the presence of several small calvarium lytic lesions. The patient's family made the decision to focus on comfort measures, and the patient died subsequent to a cardiac arrest on hospital day 17.

In their analysis of the adverse event, the authors point out that bisphosphonates are generally well tolerated with occasional adverse effects of hypocalcemia, nephrotoxicity, pancytopenia, and osteonecrosis. They mention that the patient's renal function was normal prior to starting chemotherapy and had remained stable from the time of her diagnosis of multiple myeloma. However, 1 week after receiving zoledronic acid, the patient developed acute renal failure. The authors also emphasize that hypovitaminosis D and concurrent dexamethasone and zoledronic acid administration have been identified as independent risk factors for severe hypocalcemia when metastatic tumors are treated with zoledronic acid. The authors state, "Corticosteroids decrease blood calcium levels by suppression of intestinal calcium absorption, depression of vitamin D activity and resorption of calcium in renal tubules." The authors also mention that there have been case reports (Singh D, et al) concerning patients with multiple myeloma with unrecognized vitamin D deficiency who developed hypocalcemia following zoledronic acid administration that improved only after the administration of vitamin D replacement.

The authors warn that careful clinical and biochemical evaluation is required before administration of bisphosphonates in cancer to avoid undesired adverse effects. They recommend that vitamin D levels should be a part of screening before administration of a more potent and longer acting bisphosphonate such as zoledronic acid.

Aldave APN, Jaiswal S. Severe resistant hypocalcemia in multiple myeloma after zoledronic acid administration: A case report. *J Med Case Rep.* 2014;8:353

Dingh D, Khaira NS, Sekhon JS. Symptomatic hypocalcemia after treatment with zoledronic acid in a patient with multiple myeloma. *Ann Oncol.* 2004;15(12):1848.

ZONISAMIDE-INDUCED ACUTE KIDNEY INJURY

A 33-year-old Caucasian male was seen in the emergency department following status epilepticus and loss of consciousness. The patient's home maintenance medications were phenytoin 100 mg in the morning and 300 mg at bedtime, zonisamide (*Zonegran*) 200 mg daily, loratadine 10 mg daily, naltrexone 50 mg daily, and propranolol ER 120 mg daily. Laboratory results indicated the patient had a serum creatinine of 1.2 mg/dL (normal value, 0.5-1.2 mg/dL), BUN 12 mg/dL (normal value, 16-23 mg/dL), lactate level 2.9 mmol/L (normal value, 0.5-2.2 mmol/L), total phenytoin level of 6.9 µg/mL (normal value, 10-20 µg/mL), and an albumin level of 4.3 g/dL (normal value, 3.5-5 g/dL). The patient was then loaded with 1000 mg of phenytoin intravenously.

The patient was maintained on his usual maintenance dosage of phenytoin and his zonisamide was increased to a total daily dose of 500 mg (200-100-200 mg). The patient was extubated on day 2 without complications. His lab values on day 2 were the following: creatinine phosphokinase (CPK) 542 U/L (normal value, 25-150 U/L), serum creatinine 2.8 mg/dL, and BUN 23 mg/dL. The patient's zonisamide was discontinued on day 3 because of continued evidence of intrinsic kidney injury including fractional excretion of sodium (FE_{Na}) of 2.6%. A FE_{Na} of greater than 1% but less than 4% indicates intrinsic kidney injury. Additionally the patient's total phenytoin level had risen to 23.5 µg/mL and lacosamide 50 mg twice daily was initiated as an adjunctive seizure medication. The patient's clinical course was complicated by a pulmonary infection that was treated successfully. On hospital day 6, the patient had a serum creatinine of 1.3 mg/dL and BUN 12 mg/dL. He was discharged on his previous dosage of phenytoin, lacosamide 50 mg twice daily, which was to be increased to 3 times daily after 1 week, and a 3-day regimen of levofloxacin 500 mg daily. While the patient was an outpatient, at some time he was restarted on zonisamide. The reason for the reinitiation of zonisamide was unclear.

The patient presented to the emergency room again with status epilepticus 10 months after his last admission, and he was intubated and managed in a similar fashion. The patient's maintenance medications were unchanged since his last admission except for zonisamide 400 mg daily (100-100-200 mg). The patient's labs on admission were serum creatinine 0.9 mg/dL, BUN 11 mg/dL, and a total phenytoin level of 10.5 µg/mL. The patient's current episode of status epilepticus was thought to be due to nonadherence and a possible infectious cause. The patient was started on broad-spectrum antibiotics and the doses of his antiepileptic medications were increased. On hospital day 2, the new zonisamide dosage was 600 mg daily (200-200-200 mg) and phenytoin was increased to 125 mg twice daily. Labs drawn later on day 2 revealed a serum creatinine of 4.7 mg/dL, BUN 49 mg/dL, and CPK 4410 U/L.

Zonisamide was discontinued due to suspected kidney injury, and the patient received one session of hemodialysis on hospital day 3 in conjunction with intravenous fluid hydration. The patient was initiated in levetiracetam 500 mg twice daily. An ultrasound of the kidneys revealed right-sided perinephritis. The patient's kidney function was monitored closely, and additional dialysis sessions were not necessary. The patient was extubated on hospital day 3, but he did have a subsequent pulmonary infection that required therapy. The patient was discharged on day 18 with complete resolution of his kidney injury with a serum creatinine of 1.1 mg/dL and BUN of 9 mg/dL. His seizure disorder was managed with phenytoin 100 mg 3 times daily and levetiracetam 500 mg twice daily.

The authors summarize that zonisamide is the likely cause of the patient's 2 episodes of acute renal failure based on the temporal relationship of the upward dosage titration of zonisamide. They also state that after review by multiple clinicians, the patient's concomitant medications were unlikely to have caused his renal failure. The authors also state, "The detrimental effects of up-titration of zonisamide were likely perpetuated by volume depletion and rhabdomyolysis from seizure activity." The authors identified one previously reported case of acute kidney injury occurring with zonisamide (Fujita Y, et al). The authors noted that clinicians should be aware of this potential adverse effect and renal function should be closely monitored when patients are started on zonisamide or if they have an upward titration of their dosage. In closing, the authors make an excellent point: "…this case speaks to the important of accurate medication reconciliation procedures in ensuring safe continuation of therapy." This case also points to the importance of accurate transition of care procedures for inpatients and outpatients as evidenced by the fact that the patient was restarted on zonisamide as an outpatient after his first episode of acute renal failure.

Dixit D, Stewart D, Bridgeman MM, et al. Zonisamide-induced acute kidney injury. *Epilepsy Behav Case Rep.* 2015;3:23-25.

Fujita Y, Hasegawa M, Nabeshima K, et al. Acute kidney injury caused by zonisamide-induced hypersensitivity syndrome. *Intern Med*. 2010;49:409-413.

PSYCHOSIS ASSOCIATED WITH GUANFACINE

A 5-year-old African American male with attention deficit hyperactivity disorder (ADHD) presented with new-onset visual and tactile hallucinations of snakes. The patient awoke from sleep in the middle of the night and was communicative and coherent but agitated during the episodes, which persisted into the day time. The patient had been started on 1 mg of long-acting guanfacine (*Intuniv*) daily 2 weeks earlier. Six days prior to the patient's hallucinations, his dosage had been increased to 2 mg daily. After the symptoms occurred, the patient's mother decreased the guanfacine dosage back to 1 mg daily and brought the child to the hospital.

The patient's basic metabolic panel, serum and urine toxicology, and EKG were all normal. An MRI of the brain also was normal. The patient had no prior history of hallucinations or family history of psychiatric illness. The patient was managed with total doses of 3.5 mg of haloperidol and 1.5 mg of lorazepam. The patient's long-acting guanfacine was discontinued and his psychotic symptoms resolved over the next 3 days.

The authors report that there have been a number of prior cases in adults when alpha-agonists have caused hallucinations and/or delirium. However these case reports predominantly concerned the use of clonidine. The authors state, "The psychoactive properties of alpha adrenergic agonist derive from their effects on the noradrenergic system. Alpha agonists can suppress arousal via stimulation of presynaptic autoreceptors in the locus coeruleus. An acute alteration in arousal may elicit anxiety and hallucinations." The authors warn that although this adverse effect is admittedly rare, it is important that psychotic symptoms be considered as potential adverse effects of alpha-agonist therapy.

Kim RK, Chayer R. Psychosis associated with guanfacine. *J Clin Psychopharmacol*. 2015;35(2):213. ■