ISMP Adverse Drug Reactions

Nonconvulsive Status Epilepticus in Elderly Patients Receiving SSRIs

Euglycemic Diabetic Ketoacidosis Associated with Canagliflozin Use in a Type 1 Diabetic Patient

Duloxetine-Induced Galactorrhea

Canagliflozin-Associated Severe Hypercalcemia and Hypernatremia

Vemurafenib-Induced Fanconi Syndrome

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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.

NONCONVULSIVE STATUS EPILEPTICUS IN ELDERLY PATIENTS RECEIVING SSRIS

Nonconvulsive status epilepticus (NCSE) is a prolonged epileptic condition in which patients exhibit a diminished level of consciousness and behavioral and/or mental abnormalities but without major convulsive movement, however the patients will exhibit epileptiform discharges on electroencephalography (EEG). It is challenging to detect this condition especially in elderly patients, because the clinical symptoms may be very subtle and may be present in patients who have preexisting dementia or other central nervous system (CNS) comorbidity.

A series of 3 cases are reviewed in elderly male patients receiving serotonergic antidepressant medications who experienced NCSE. The first patient is a 76-year-old male who was treated with paroxetine 10 mg daily for depression. Two days after his paroxetine dosage was increased to 20 mg daily, the patient developed a tremor in both of his upper limbs and episodic disturbances of consciousness with impaired dexterity. An EEG revealed the patient had impaired consciousness. He received diazepam 2.5 mg intravenously, and his EEG abnormalities resolved. Paroxetine was discontinued and phenytoin was initiated, which resulted in complete resolution of the patient's

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impaired consciousness. The patient's symptoms did not recur even after his phenytoin was discontinued, and he did not have a relapse of NCSE during 7 years of follow-up.

The second case occurred in a 73-year-old male who was receiving sertraline 50 mg daily and mirtazapine 15 mg daily. The patient began to respond poorly to conversation and occasionally stopped during movement with a vacant stare. His symptoms occurred 5 days after his mirtazapine dosage was increased to 30 mg daily. When he was taken to the emergency department, he exhibited myoclonus and tremor resembling catatonic symptoms. He received 5 mg of diazepam intravenously, and his symptoms and his abnormal EEG findings resolved. It was then noted that the patient had exhibited similar symptoms 4 years earlier when he received amitriptyline 100 mg daily. The patient was then placed on phenobarbital for NCSE, and his sertraline and mirtazapine were tapered off. Eventually his phenobarbital was discontinued. The patient has not had a recurrence of NSCE in over 2 years. The third patient had a similar clinical course to the first 2, with the offending agent being sertraline.

The authors warn that due to the difficulty in diagnosing NCSE, this condition is probably under-recognized in clinical practice. A delay in NCSE diagnosis and prolonged seizure activity may lead to aspiration pneumonia, falls, and other accidents, which can all be associated with increased morbidity and mortality. The authors recommend that "when such medication is commenced in the elderly, that the patient be monitored closely for impaired awareness and, if this is observed, that EEG monitoring be performed to determine whether this is attributable to NCSE."

Taniguchi G, Miyajima M, Watanabe M, et al. Nonconvulsive status epilepticus in the elderly associated with newer antidepressants used at therapeutic doses: A report of three cases. *Epilep Behav Case Rep.* 2015;3:8-11.

EUGLYCEMIC DIABETIC KETOACIDOSIS ASSOCIATED WITH CANAGLIFLOZIN USE IN A TYPE 1 DIABETIC PATIENT

A 43-year-old male with type 1 diabetes was seen in the emergency department after complaining of 5 hours of malaise, nausea, multiple vomiting episodes, and restlessness. The patient reported that he had measured his blood glucose and it was 117 mg/dL (normal fasting value, 65-110 mg/dL) before coming to the emergency department. While the patient was

being examined, he became restless, diaphoretic, and tachycardic. Over the first hour, he was given 2 L of normal saline solution (NSS), ondansetron 4 mg for nausea, and lorazepam 1 mg for his restlessness; however his heart rate remained 120 bpm. The patient's initial laboratory results were blood glucose of 139 mg/dL, serum bicarbonate 14 mEq/L (normal value, 22-26 mEq/L), serum creatinine 0.9 mg/dL (normal value, male, 0.8-1.4 mg/dL), anion gap 15 mmol/L (normal value, 3-11 mmol/L), and white blood cell count (WBC) 19.1 K/ μ L (normal value, 4.1-10.9 K/ μ L). The patient was then given an additional liter of NSS and repeat labs were ordered.

The results of the repeat labs were glucose 207 mg/dL, potassium 6.7 mEq/L (normal value, 3.5-5 mEq/L), serum bicarbonate 10 mEq/L, serum creatinine 1.4 mg/dL, anion gap 11, lactic acid, venous 1.9 mmol/L (normal value, 0.5-1.5 mmol/L), and serum ketones 8.3 mmol/L (normal value, <0.1 mmol/L). The patient was then treated for hyperkalemia, and a venous blood gas was drawn with the following results: VpH 7.15 (normal value, 7.32-7.43), VPCO₂ 28.8 mm Hg (normal value, 40-60 mm Hg), and bicarbonate 10.1 mEq/L. The patient was then further hydrated and a repeat venous blood gas revealed worsening acidosis with a VpH of 7.08.

At this time, the patient was set to be transferred to the intensive care unit; the emergency room physician suggested treatment with an insulin drip and dextrose for suspected diabetic ketoacidosis (DKA). The ICU physician did not feel that insulin should be administered, because the patient was not clearly in DKA. The patient was then questioned about alcohol use or any other drug ingestion he may have had, and he said he was taking canagliflozin (*Invokana*). An endocrinologist was consulted and recommended dextrose 5% with one-half NSS (D5/1/2NSS) and an insulin drip to correct the patient's acidemia. The patient was admitted to the ICU and the insulin drip and D5/1/2NSS were initiated. The patient's acidemia rapidly corrected. The patient was discharged from the hospital 2 days later.

Canagliflozin is an inhibitor of sodium-glucose cotransporter 2 (SGLT-2 inhibitor), which is responsible for 90% of glucose reuptake from the glomerular filtrate. Inhibition of SGLT-2 allows for increased glucose excretion independent of insulin secretion. This medication was only tested in type 2 diabetics, however this patient was a type 1 diabetic who lacks insulin production. The authors point out that the decision to prescribe this medication to a type 1

diabetic is dangerous. The patient's initial blood glucose was below 150 mg/dL and his serum bicarbonate was 14 mEq/L. The patient's relative acidemia was not fully explained by his presentation and history. The emergency room physician's continued questioning about additional medications the patient may have received finally led to the solution. While the patient was acidotic, his blood glucose was below 150 mg/dL because of the canagliflozin he was receiving, which does not work by an insulin-dependent mechanism. The addition of canagliflozin obviously clouded the picture of DKA in this patient.

The authors' state, "Off-label medication use is a precipitous and precarious cliff that we often carelessly tread. It is the responsibility of the physicians as a whole to practice safe and informed prescribing of medications, as the implications of medication misuse are far reaching and in some cases fatal."

St Hilaire R, Costello H. Prescriber beware: Report of adverse effect of sodium-glucose cotransporter 2 inhibitor use in a patient with contraindication. *Am J Emerg Med.* 2015;33:604.e3-604.e4.

DULOXETINE-INDUCED GALACTORRHEA

A 28-year old female presented to a neurology clinic with migraine-type headache and a spontaneous discharge of milk-like secretions from both of her breasts. A medication history revealed she was receiving duloxetine (*Cymbalta*) 30 mg daily for her migraines for the past 4 months. The patient reported that after 6 weeks of treatment, her migraine symptoms had decreased but at week 10 her galactorrhea began. She had not received any other medications in the past. The patient did not have a history of endocrine or reproductive pathology, previous surgery, or alcohol or other substance abuse. She was not currently having her menstrual period and a pregnancy test was negative.

The patient then underwent a complete examination and laboratory work-up. Her serum prolactin level was normal 8.05 ng/mL (normal value, 4.8-23.4 ng/mL), which was unexpected. Patients presenting with galactorrhea typically have an elevated prolactin level. The patient's prolactin level remained normal upon repeated measurements over time. Additional laboratory tests were within normal limits and included complete blood count, liver function test, kidney function tests, thyroid function tests, cortisol, follicle stimulating hormone, luteinizing hormone, and estradiol. An ultrasound of the breast and an MRI of the brain were normal. A cytological

examination of secretion from the breasts revealed no inflammation and the secretions were not consistent with cystic fluid. Based on the lack of an alternate explanation for the patient's galactorrhea, the investigators concluded that it was due to her use of duloxetine.

The patient's duloxetine treatment was discontinued and her breast discharge ceased after 3 days. Follow-up serum prolactin levels at 1 week and 4 weeks after discharge remained within normal limits. The patient was prescribed propranolol for treatment of her migraine headaches. Over the next 6 months, her migraine management was successful with no recurrence of galactorrhea.

The authors discussed the possible mechanisms by which an antidepressant could cause galactorrhea. They point out that galactorrhea is often associated with an increased prolactin level. They state, "Hyperprolactinemic galactorrhea due to antidepressant drugs affect postsynaptic serotonin receptors in the hypothalamus which are stimulated directly or that tuberoinfundibular dopaminergic neurons are inhibited through serotonin indirectly." The authors mention that preliminary research suggests normal prolactin galactorrhea could be due to hyperresponsiveness of thyrotropin-releasing hormone. However, the patient in this case had normal thyroid function tests.

In closing, the authors warn that in a patient with galactorrhea with normal prolactin levels, clinicians should consider duloxetine as a possible cause of galactorrhea.

Demirci S, Unubol M, Demirci K. Galactorrhea with normal prolactin levels associated with duloxetine. *J Clin Psychopharmacol.* 2015;35(3):346-347.

CANAGLIFLOZIN-ASSOCIATED SEVERE HYPERCALCEMIA AND HYPERNATREMIA

A 60-year-old male with type 2 diabetes was admitted to the hospital with altered mental status after a syncopal episode. A medical history for the patient included primary hypothyroidism and hypertension as well as type 2 diabetes. A medication history revealed that the patient was receiving insulin, glimepiride, metformin, and canagliflozin (*Invokana*). The patient also reported ingesting 8 to 10 Tums daily for heartburn for the past week. Clinical labs were drawn on the patient, and they revealed the following abnormalities: calcium 17.4 mg/dL (normal range, 8.9-10.3 mg/dL), serum urea nitrogen (BUN) 37 mg/dL (normal range, 6-20 mg/dL), serum

creatinine 1.91 mg/dL (normal range, 0.64-1.27 mg/dL), glucose 407 mg/dL (normal range, 70-100 mg/dL), bicarbonate 12.1 mmol/L (normal range, 24-28 mmol/L), and a β -hydroxy butyrate 9.2 mmol/L (normal range, 0.02-0.27 mmol/L). Based on the lab results, the patient was diagnosed with diabetic ketoacidosis (DKA). Additional lab tests revealed that the patient had low levels of parathyroid hormone as well as vitamin D, however he had a normal thyroid-stimulating hormone level.

The patient was treated with calcitonin, pamidronate, subcutaneous insulin, and intravenous hydration with normal saline. This treatment resolved the patient's DKA within 24 hours. The patient's hypercalcemia and renal function improved over 48 hours, however his serum sodium increased from 129 mmol/L to 162 mmol/L (normal range, 135-147 mmol/L). This increase in serum sodium continued to occur even with the change from normal saline to 0.45% saline intravenously. A urine analysis revealed urine sodium of less than 10 mEq/L (a prerenal cause), a urine glucose of greater than 1000 mg/dL (normal result is negative), and a urine osmolality of 782 mOsm/kg (reference range, 50-1200 mOsm/kg). The patient's serum osmolality was 352 mOsm/kg (reference range, 275-299 mOsm/kg).

Over the next 2 days, the patient's hyponatremia slowly resolved with the continued administration of hypotonic intravenous fluids and free water administered via a nasogastric tube. The patient's mental status also improved over this time. The patient's urinary glucose excretion remained elevated at greater than 1000 mg/dL 4 days after the discontinuation of canagliflozin, even with the resolution of his hyperglycemia.

In evaluating the possible causes for the patient's hypercalcemia, the authors suggest multiple factors. They state, "First the patient had ingested excessive calcium antacid tablets over the past week. Second, osmotic diuresis, poor oral intake and hyperglycemia led to dehydration.... Lastly, intestinal and urinary calcium absorption may have been increased due to inhibition of SGLT1 by the drug."

It has been demonstrated that inhibition of intestinal SGLT1 can lead to increased calcium absorption. The authors also assess the possible cause of the patient's severe hyponatremia. They state, "Severe hyponatremia following saline hydration may be due to osmotic diuresis, which can cause hypernatremic dehydration due to electrolyte-free water loss and possibly hyperaldosteronism from intravascu-

lar volume depletion." The authors theorize that the SGLT2 inhibitor caused an osmotic diuresis in this patient leading to her hyponatremia. They suggest that the mechanism by which SGLT2 inhibitors affect free water loss should be studied further.

The authors warn that SGLT2 inhibitors may cause hypercalcemia in susceptible patients, possibly by causing dehydration from osmotic diuresis; increased calcium absorption may play a role. They also recommend that serum calcium levels should be monitored in patients receiving SGLT2 inhibitors who are elderly, have established hypercalcemia, or take oral calcium supplementation.

Kaur A, Winters S. Severe hypercalcemia and hyponatremia in a patient treated with canagliflozin [published online ahead of print June 5, 2015]. *Endocrinol Diabetes Metab Case Rep*. 2015;2015:150042. 10.1530/EDM-15-0042.

VEMURAFENIB-INDUCED FANCONI SYNDROME

A male in his 70s was initiated on vemurafenib (*Zelboraf*) 960 mg twice daily as a first-line treatment for stage IV melanoma with BRAF mutation V600K and metastasis to his liver and lymph nodes. On the ninth day of vemurafenib therapy, the patient developed a fever of 101.5°F, an erythematous maculopapular eruption with rough patches, and small, acne-like bumps on all 4 of his limbs and trunk involving 30% of his body surface area. He also experienced photosensitivity of his face. The patient's vemurafenib dosage was then decreased to 720 mg twice daily. Laboratory tests drawn at this time revealed a WBC of $12 \times 10^9/L$ with 12% eosinophils and 2% atypical lymphocytes. However the patient's liver enzymes remained within normal limits.

On day 12 of vemurafenib therapy, laboratory tests revealed hypokalemia with excessive kaliuresis that persisted in spite of potassium supplementation. Additional tests revealed urinary excretion-associated hyperphosphaturia and hyperuricuria, while blood tests revealed hypophosphatemia and hypouricemia. The patient's glomerular filtration rate (GFR) remained stable at 101 mL/min/1.7 m². These findings lead to the diagnosis of Fanconi syndrome. Fanconi syndrome is a disease of the proximal renal tubules of the kidney in which glucose, amino acids, uric acid, potassium, phosphate, and bicarbonate pass into the urine, instead of being reabsorbed back into the bloodstream.

The patient's skin eruptions and eosinophilia decreased gradually until normalization on day 16 of therapy. On day 19, vemurafenib therapy was

discontinued. Within 7 days, the patient's fever had improved and his electrolyte profile had normalized. A tumor assessment at this time revealed a major tumor response. Because of the major tumor response, vemurafenib was reinitiated at half of the initial dosage on day 29. Within 21 days of vemurafenib reinitiation, the patient experienced a relapse of hypokalemia and hypouricemia with acute urinary loss but without a recurrence of the skin eruptions or eosinophilia. Vemurafenib was stopped at this time, and the patient's electrolyte abnormalities normalized within 5 days. Treatment was then begun with dabrafenib, another BRAF inhibitor. After 5 months of treatment with dabrafenib, the patient has not had a recurrence of his adverse events.

The authors point out that in this case, they did not observe all of the possible renal losses that can

occur in Fanconi syndrome; but they also point out that all of these losses do not occur in most Fanconi syndrome cases. Their patient experienced a loss of potassium, phosphate, and uric acid. They also surmise that although the patient did not experience a decrease in GFR, this suggests that vemurafenib exerts tubular toxic effects. They also mention that the patient's skin eruptions and eosinophilia should be considered a different set of adverse effects unrelated to the Fanconi syndrome, because the skin manifestations did not recur when vemurafenib was reinitiated. The authors recommend that patients receiving vemurafenib therapy should have regular blood electrolyte monitoring.

Denia D, Franck N, Fichel F, et al. Fanconi syndrome induced by vemurafenib: A new renal adverse event. *JAMA Derm.* 2015;151(4):453-454. ■