ISMP Adverse Drug Reactions

Dalfampridine-Induced Seizures

Efavirenz-Induced Hypersomnolence Leading to Coma and Death

Cerebral Toxoplasmosis with Rituximab

Torsades de Pointes after Low-Dose Aripiprazole

Atypical Antipsychotic-Induced Sleepwalking

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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.

DALFAMPRIDINE-INDUCED SEIZURES

A 50-year-old woman presented with new-onset generalized tonic-clonic seizure 4 days after being started on dalfampridine (*Ampyra*) 10 mg twice daily and donepezil 5 mg daily simultaneously. One hour after the patient's eighth dose of dalfampridine, her husband found her having a generalized tonic-clonic seizure. She had a history of secondary progressive multiple sclerosis, and her only concurrent chronic medications were glatiramer and baclofen. The patient had no personal or family history of seizures.

During the patient's hospital stay, her electroencephalogram (EEG) showed no frank epileptiform activity. Magnetic resonance imaging (MRI) demonstrated atrophy, small vessel disease, and symmetric ventriculomegaly with no evidence of mass or recent infarct. The patient had a longstanding history of recurrent

urinary tract infections, however the results of her urinalysis did not demonstrate an infection.

Dalfampridine was immediately discontinued on her admission; once she was medically stable, she was transferred to an acute inpatient rehabilitation unit. The patient did not experience further seizure activity during her hospitalization and throughout her 2 years of follow-up. During this time, no further doses of dalfampridine were administered.

Dalfampridine is a potassium channel blocker indicated to improve walking in patients with multiple sclerosis. This medication is contraindicated in patients with a history of seizures, because of an increased incidence of seizures observed in clinical trials with dalfampridine. In clinical trials, seizures were primarily experienced at the dose of 20 mg twice daily in studies that were 9 to 14 weeks in duration. It is unclear if any

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patients experienced seizures after a shorter duration of dalfampridine administration, as this patient did during her fourth day of dalfampridine.

The authors suggest that the increased risk of seizures associated with dalfampridine may be higher than previously thought. Seizures may present at lower doses and at a shorter duration of dalfampridine therapy than previously demonstrated in clinical trials. The authors warn that dalfampridine must be used cautiously and should not be introduced at the same time as other medications that could potentially reduce the seizure threshold.

Farag A, Averill FA. Dalfampridine. Is the seizure risk greater than previously thought? *Am J Phys Med Rehabil.* 2013;92(7):635-636.

EFAVIRENZ-INDUCED HYPERSOMNOLENCE LEADING TO COMA AND DEATH

The authors report a case of progressive neuropsychiatric adverse effects demonstrated over approximately 5.5 months that eventually led to coma and death of the patient.

A 38-year-old Zimbabwean man presented to a hospital in Cape Town, South Africa. He was found to be HIV positive with a CD4 count of 58 cells/mm³ and to have biopsy-confirmed HIV-associated nephropathy with an estimated creatinine clearance of 20 mL/min. His initial HIV regimen was stavudine, lamivudine, and nevirapine. He received this regimen for 3 months. Upon routine liver function test (LFT) monitoring, it was discovered he had an increased alanine aminotransferase of 561 IU/L (reference range, 5-40 IU/L). Nevirapine was discontinued, and his LFTs improved within 5 days; at that time, efavirenz (*Sustiva*) 600 mg daily was initiated in place of nevirapine. The patient was seen a week later, and he complained of new onset headaches and lightheadedness. The patient at follow-up 1 month after efavirenz initiation complained of very vivid and unpleasant dreams in the early hours of the morning and a hangover-type sensation when he awoke. The patient also presented with a productive cough and a 4 kg weight loss. A sputum sample was negative, but a sputum culture was positive for *Mycobacterium tuberculosis*. The patient was initiated on rifampicin, isoniazid, pyrazinamide, and ethambutol.

When the patient returned more than a month later, he complained of mental slowing and a sensation of being confused when he woke up. He reported that the symptoms improved somewhat during the day. On examination, he was slow, apathetic, and slightly ataxic. He scored a 6/12 on the International HIV/AIDS Dementia Scale. A computed tomography (CT)

scan of his brain showed mild generalized cerebral atrophy, but no detectable pathology.

Nine days later, the patient presented to the hospital complaining of being sleepy all the time. He was still oriented, but he took a long time to answer questions. The patient was released to home. Three days later, he was brought back to the hospital in an extremely drowsy state. He still could answer questions, however there was a 3-second gap between questions and his response and he was too unsteady to walk at this time. A sample of his cerebrospinal fluid was obtained and was found to be normal and devoid of bacteria, fungi, and mycobacteria. His LFTs, thyroid stimulating hormone (TSH), calcium, B12, and glucose were found to be normal, however his estimated creatinine clearance was found to be 23 mL/min. Efavirenz and isoniazid were changed to nevirapine and ofloxacin, respectively, and pyridoxine 100 mg daily was administered.

In spite of these interventions, the patient continued to become more and more drowsy. The next day, the patient was unable to swallow normally and his Glasgow Coma Scale had dropped to 8/15. The patient was then transported to a tertiary hospital where he died the following day.

A postmortem examination was performed and revealed extensive aspiration pneumonia. His brain showed extensive axonal vacuolopathy, including his cerebellum. Immunoreactivity for HSV-1, HSV-2, varicella zoster virus, HIV, and cytomegalovirus were negative. The patient's plasma efavirenz concentration 5 days after discontinuation of efavirenz was 13.7 mcg/L; the recommended range for efavirenz trough concentrations is 1 to 4 mcg/L.

The authors report that efavirenz-induced hypersomnolence leading to coma and death has not previously been reported. The authors indicate that a large number of medications and toxins can cause vacuolar axonopathy. This is thought to be secondary to a toxic effect on mitochondria. Efavirenz has been shown to result in mitochondriopathy, but thus far this has been found to occur mainly in hepatocytes.

The incidence of efavirenz-induced neuropsychiatric side effects is correlated with plasma concentrations. Elevated concentrations are correlated to the cytochrome P450 isoenzyme 2B6 G>T polymorphism, among other factors. A high proportion of Southern Africans have this polymorphism and are at increased risk of severe neuropsychiatric side effects of efavirenz. In addition to this case report, the authors have encountered 3 patients who had efavirenz-induced extreme drowsiness with efavirenz trough concentrations

greater than 16 times above the upper limit of normal trough concentrations. All 3 of these patients responded well to dose adjustment of efavirenz or drug switching.

The authors recommend that clinicians be aware of this side effect; they should measure efavirenz concentrations when patients manifest severe and prolonged neuropsychiatric side effects and reduce the dose when levels are above the recommended trough range. It should be noted that efavirenz is available as a single entity product (*Sustiva*) and is also present in the combination product *Atripla* with emtricitabine and tenofovir.

Keynon C, Mfolozi S, Croxford R, et al. Severe efavirenz-induced vacuolar axonopathy complicated by fatal aspiration pneumonia. *Br J Clin Pharmacol*. 2013;74(6):1070-1072.

CEREBRAL TOXOPLASMOSIS WITH RITUXIMAB

A 71-year-old woman presented with cutaneous ulcerations on her legs. The patient was not taking any medications and had no history of infections. A skin biopsy and an exhaustive diagnostic work-up revealed cutaneous necrotizing vasculitis associated with type I essential cryoglobulinemia. The patient was then treated with oral prednisone 60 mg daily with intravenous pulses of methylprednisolone 500 mg for 3 days and azathioprine 150 mg daily for 3 months, which were all deemed unsuccessful. Because of uncontrolled vasculitis, off-label therapy with a single cycle of 4 weekly infusions of rituximab (*Rituxan*) at a dose of 375 mg/m² was administered, azathioprine therapy was discontinued, and prednisone was tapered to 50 mg daily, followed by a gradual tapering of 5 mg monthly. This new regimen resulted in complete healing of the skin ulcers within 8 weeks.

Four months after completion of rituximab therapy, the patient experienced speech disturbances, behavioral changes, and weight loss. A brain MRI showed evidence of lesions suggestive of cerebral toxoplasmosis. Cerebral toxoplasmosis was confirmed by means of a polymerase chain reaction test for *Toxoplasma gondii* DNA in the cerebral spinal fluid and the identification of bradyzoites in brain tissue. The patient was seronegative for HIV and had a normal neutrophil count 4,380/ μ L (reference range, 1,800-7,800/ μ L), normal CD4 lymphocyte count of 434 cells/mm³ (reference range, 400-1,400 cells/mm³), and normal CD8 lymphocyte count of 376 cells/mm³ (reference range, 160-880 cells/mm³). The patient tested positive for *Toxoplasma*-specific IgG but negative for IgM, which is suggestive of the reactivation of disease from

a prior infection. Despite treatment with pyrimethamine, sulfadiazine sodium, and folinic acid, the patient's mental status did not improve.

The authors point out that treatment with rituximab results in a rapid depletion of CD20 B cells, which remain at low or undetectable levels for 2 to 6 months before returning to pretreatment levels, generally within 12 months. Particularly low serum IgG levels after rituximab treatment are associated with a significantly increased risk of serious infections, with an almost 2-fold increase in risk. While the relationship between rituximab and parasitic infections remain unclear, there has been a single report of granulomatous *Acanthamoeba* encephalitis and an increased risk of persistent and relapsing babesiosis.

The authors urge clinicians to consider cerebral toxoplasmosis in any patient receiving rituximab with new cognitive or neurologic deficits. They also recommend the screening of patients for *Toxoplasma* infection, however the need for primary prophylaxis against toxoplasmosis in patients who test positive for *Toxoplasma*-specific IgG prior to the use of rituximab remains to be determined and should be evaluated for each patient with a low IgG level.

An invited commentary was included in the journal immediately following this case report. Dr. Linos, who authored the commentary, points out that although rituximab has helped many patients with lymphoma and rheumatoid arthritis, it has been linked to several major infectious complications. Reactivation of hepatitis B, cytomegalovirus disease, and the rare but fatal progressive multifocal leukoencephalopathy are the most infamous of these infections. As more patients are prescribed rituximab, we must remain vigilant to complications and study ways to help patients and physicians make informed decisions that incorporate the rapidly expanding evidence base concerning potential adverse effects.

Safa G, Darrieux L. Cerebral toxoplasmosis after rituximab therapy. *JAMA Intern Med*. 2013;173(10):924-925.

Linos E. Invited commentary: Balancing the risks and benefits of rituximab. *JAMA Intern Med*. 2013;173(10):926.

TORSADES DE POINTES AFTER LOW-DOSE ARIPIRAZOLE

A 42-year-old white male with a previous history of schizophrenia, diabetes, hypertension, and stroke arrived at the emergency room following 2 days of fever, chills, diarrhea, and altered mental status. He was admitted to the intensive care unit (ICU) and treated for sepsis. During his time in the ICU, his clinical course was complicated with renal failure, adrenal insufficiency,

and acute respiratory distress syndrome. One week into the patient's hospital stay, he was exhibiting symptoms thought to be related to hypoactive delirium, schizophrenia, or both. The patient's medication prior to admission, quetiapine 400 mg daily at bedtime, was restarted, but it was discontinued after 1 dose when the QTc interval was discovered to be 644 milliseconds. The only prior electrocardiogram (ECG) was obtained upon arrival at the emergency department 7 days earlier, and it revealed a QTc interval of 528 milliseconds. The authors point out that a QTc interval greater than 450 milliseconds for men and 470 milliseconds for women indicates prolongation, with QTc intervals greater than 500 milliseconds or a change from baseline that exceeds 60 milliseconds being considered clinically significant.

Twenty-three days after the dose of quetiapine and resolution of the patient's acute illness, a new baseline QTc of 414 milliseconds was documented. In light of the QTc changes caused by quetiapine, aripiprazole (*Abilify*) 2.5 mg daily was started, because of the data supporting its minimal effect on the QTc interval. After receiving 5 days of aripiprazole, the patient had a cardiac arrest due to torsades de pointes, which was documented via ECG. Minutes prior to the cardiac event, an ECG recorded a QTc interval of 624 milliseconds. The patient was resuscitated with medication and electrical shock and returned to normal sinus rhythm. Aripiprazole was discontinued at this time.

A cardiac catheterization was performed and revealed no significant disease. Follow-up QTc measurements on days 1, 5, and 14 after aripiprazole discontinuation were 537, 472, and 450 milliseconds, respectively. The patient's QTc interval returned to normal over 14 days, which is possibly related to the 75-hour half-life of aripiprazole.

The patient had no prior documentation of a congenital long QT syndrome. The only risk factor for QTc prolongation and torsades de pointes was concomitant intravenous famotidine 20 mg daily, however the patient continued to receive famotidine after the cardiac event without incident. Additionally, significant renal impairment is an important factor in famotidine-induced QTc prolongation, and the patient's estimated creatinine clearance was greater than 60 mL/min.

The authors suggest that clinicians should be aware that low-dose aripiprazole may produce significant QTc prolongation and torsades de pointes in patients with minimal risk factors. Because aripiprazole may be selected

for patients with a history of QTc interval prolongation or a high baseline interval, more cardiac data are needed to assess the safety of aripiprazole in this population.

Nelson S, Leung JG. Torsades de pointes after administration of low-dose aripiprazole. *Ann Pharmacother*. 2013;47:e11.

ATYPICAL ANTIPSYCHOTIC-INDUCED SLEEPWALKING

A 52-year-old man with bipolar disorder was admitted to the hospital with a manic episode in November 2011. He had taken valproate 3,000 mg daily and carbamazepine 1,000 mg daily for the past year, prior to admission. In the emergency room, asenapine (*Saphris*) was added to his regimen and the dose was gradually increased over 2 weeks to 15 mg daily. After 2 weeks, the patient was observed sleepwalking for 45 minutes; he wandered around his room, tidied it, organized his clothes, and then went back to sleep. The patient was very disturbed by this event and wanted to be taken off of asenapine, and it was discontinued at that time.

A year prior to the patient's current admission, he had a similar episode of sleepwalking when quetiapine 600 mg daily was added to the mood stabilizers he was receiving (valproate and carbamazepine). The patient also had sleepwalking episodes in August 2000 while receiving olanzapine 15 mg daily and lithium 1,800 mg daily. In both cases, sleepwalking subsided immediately after the treatment with the antipsychotic medication was stopped. The patient was screened for pathology after the sleepwalking episodes via a CT scan and EEG. Neither test indicated pathology. Other antipsychotic medications, risperidone and ziprasidone, did not cause sleepwalking, but they were not effective at preventing this patient's manic episodes.

The authors point out that this is the first case of three different atypical antipsychotic medications causing somnambulism in the same patient, and this occurrence implies a class effect of this group of medications. This is also the first case of sleepwalking documented with the use of asenapine. The authors speculate about the mechanism by which atypical antipsychotic agents cause somnambulism but note that the mechanism has not fully been elucidated at this point. They note that it is important to be aware of this possible side effect, as it might endanger the patient.

Dagan Y, Katz G. A case of atypical antipsychotic-induced somnambulism: A class effect. *J Clin Psychiatry*. 2013;74(4):370. ■