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ISMP Adverse Drug Reactions

High-Dose Loperamide Abuse Inducing Life-Threatening Cardiac Arrhythmias

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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.

HIGH-DOSE LOPERAMIDE ABUSE INDUCING LIFE-THREATENING CARDIAC ARRHYTHMIAS

The authors conducted an observational case series of 5 patients who had ingested large doses of loperamide and had experienced significant cardiac conduction abnormalities. Since loperamide is available over the counter and it is a peripheral mu-receptor agonist, it has begun to be abused recreationally and to diminish the withdrawal symptoms from opiates. In the authors' first case, a 30-year-old male came to an emergency department after multiple episodes of syncope. An ECG revealed a wide QRS interval and a QTc of greater than 500 ms. The patient's electrolytes were normal, and a comprehensive toxicology screen was negative. The patient experienced several episodes of ventricular tachycardia and cardiac arrest with successful resuscitation. He then admitted to an increasing use of up to 200 loperamide 2 mg tablets (400 mg) daily for several weeks. He stated that he was using loperamide as an opioid alternative and was not taking any other medications. A loperamide serum concentration on hospital day 2 was 22 ng/mL, which was

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3 days after his last dose. A therapeutic loperamide concentration is typically 0.24 to 1.2 ng/mL.

A second case involved a 43-year-old female who experienced multiple episodes of torsades de pointe (TdP), which did not respond to lidocaine, amiodarone, sodium bicarbonate, magnesium, and lipid rescue therapy, and more than 15 repeated cardioversions. The patient had a pacemaker inserted with overdrive pacing. Her initial QTc interval was 684 ms with frequent premature ventricular contractions. A urine drugs-of-abuse screen was obtained and was negative for opiates and methadone. The patient reported the use of 144 tablets of 2 mg loperamide (288 mg) to manage her opiate withdrawal symptoms, and she was not taking any other medications.

A third case occurred in a 28-year-old male who experienced syncope and tachycardia. The patient reported that he was receiving an unknown dose of amitriptyline and loperamide. The patient stated that he had been using an increasing dose of over 396 loperamide 2 mg tablets (792 mg) daily. His QTc was 647 ms, and his electrolytes were within normal limits. He experienced ventricular tachycardia unresponsive to multiple therapies, but it was finally controlled with the insertion of a pacemaker. His urine drug screen for 9 drugs of abuse was negative for all substances. A loperamide level measured 5 hours after his arrival at the hospital was 130 ng/mL, and amitriptyline and nortriptyline blood levels were all within normal limits. The patient's QTc remained greater than 500 ms until the 10th day of his hospitalization before normalizing. He reported that he has been abusing loperamide for 1 year and had previously been hospitalized for an unexplained syncopal episode.

A fourth patient was a 33-year-old male who had ingested 60 to 100 loperamide 2 mg tablets over the previous 6 hours as an opiate substitute, but his exact chronic loperamide dosage was unclear. EKG detected a QTc interval of 636 ms. The patient had no significant medical or medication history. His serum loperamide level was 77 ng/mL, however no additional toxicology testing was performed as the patient left the hospital against medical advice after 24 hours.

The fifth and final case reported was a 33-year-old male who came to the emergency room with anxiety, panic, and chest tightness. He had a history of alcohol and opioid abuse and had recently been abusing loperamide at a dose of 35 loperamide 2 mg tablets (70 mg) daily. However on the day of his admission, he reported that he had taken 140 mg of loperamide over the previous 7 hours. His QTc interval was 490 ms and his loperamide level was 33 ng/mL. A urine drugs-of-abuse screen was negative for methadone, opiates, and tetrahydrocannabinol and was only positive for benzodiazepines, which he had received in the emergency room.

The authors reported the 5 cases of loperamide-induced cardiac conduction disturbances because loperamide is not normally associated with cardiac conduction disturbances at usual doses. The mechanism of this adverse effect is thought to be inhibition of the HERG-coded I_{kr} channel, which is associated with QT prolongation. It seems that at the very high dosages ingested by these patients, loperamide can cause life-threatening cardiac conduction disturbances. The patients in these cases were utilizing high-dose loperamide to combat opioid withdrawal symptoms. Loperamide is a peripherally acting opioid agonist that is excluded at the blood–brain barrier by p-glycoprotein. Many of the patients were screened for possible co-ingested substances that could have accounted for the cardiac effects observed. The patient in case 3 was also screened for quinine, which is a p-glycoprotein inhibitor that is commonly co-ingested with loperamide to enhance its passage into the central nervous system.

The authors warn that with recent efforts to restrict the diversion of prescription opioids, increasing abuse of loperamide as an opioid substitute may be seen. This is especially important because loperamide-induced conduction disturbances are difficult to treat and may not respond to a number of first-line interventions.

Marraffa JM, Holland MG, Sullivan RW, et al. Cardiac conduction disturbance after loperamide abuse. *Clin Toxicol.* 2014;52:952-957.

TOPIRAMATE-INDUCED DIARRHEA IN A BREASTFED INFANT

A 31-year-old female had been receiving topiramate (*Topamax*) 100 mg daily for several years and throughout her pregnancy. She delivered a healthy female child and expressed an interest in breastfeeding. There is little definitive information about the effects of topiramate in breastfeeding, so it was thought to decrease the infant's exposure by replacing 2 breastfed meals daily with infant formula. The infant initially thrived, but by the age of 40 days she experienced diarrhea with 8 to 10 watery, foamy stools per day. The child was evaluated, and an assessment of family contacts did not reveal an obvious cause of the diarrhea. The diarrhea continued for 18 days, and the child's weight gain rate began to decline. The mother's general practitioner suspected the diarrhea was related to topiramate. Breastfeed-

ing was stopped; within 2 days, the child's diarrhea frequency was reduced to 2 to 3 stools per day and the mother observed solid feces, with smell and color returning to normal.

While breastfeeding, the mother extracted her breast milk via breast pump and stored the milk in the freezer. The milk samples were sent for analysis of topiramate content. A topiramate concentration of 5.3 µg/mL was measured. The authors calculated that with a topiramate milk concentration of 5.3 µg/mL and an estimated daily intake of 450 mL of mother's milk in an infant weighing 4735 g would equate to a daily dose of 0.5 mg/kg of topiramate. Therefore the infant would have ingested 35% of the mother's weight-adjusted topiramate dose. The authors warn that infant diarrhea increases the risk of electrolyte disturbances and a possibility of weight loss in the infant. They point out that this may be an unknown risk factor of topiramate use while breastfeeding.

Westergren T, Hjelmeland K, Kristoffersen B, et al. Probable topiramate-induced diarrhea in a 2-month-old breast-fed child – a case report. *Epilepsy Behav Case Rep*. 2014;2:22-23.

DANAZOL-INDUCED STEVENS–JOHNSON SYNDROME

A 19-year-old female came to the hospital with a 2-day history of facial rash and oral ulcers. Her medical and medication history revealed that she had a 5-year history of systemic lupus erythematosus (SLE) for which she had been receiving tacrolimus 2 mg daily and prednisolone 15 mg daily. She had been started on danazol 200 mg daily 2 weeks earlier for the treatment of autoimmune hemolytic anemia. The authors report, "The patient was febrile with dusky purpuric macules, papules and targeted lesions, over the forehead, cheeks, neck and arms. Similar papules and plaques with central bullae were seen on the palms. Erosions were noted on the lips, hard palate, and vulvae." The lesions affected 3% of her body surface area. Skin biopsy revealed findings consistent with Stevens–Johnson syndrome (SJS).

The patient's danazol was immediately discontinued and treatment was begun with intravenous (IV) methylprednisolone 1 g daily for 3 days followed by IV hydrocortisone 100 mg every 8 hours for 3 days. The patient was discharged from the hospital receiving oral prednisolone 30 mg daily, which was eventually tapered to 10 mg daily. Topical treatments with betamethasone and clioquinol were also applied.

The authors reported that the patient experienced re-epithelization within 10 days of treatment initiation. They also noted that the possibility of SJS/toxic epidermal necrolysis occurring at a higher frequency in patients with collagen-vascular disorders, however they point out that there is no clear evidence that SLE by itself is a risk factor. They warn that clinicians should be aware of this potentially severe cutaneous adverse reaction with the use of danazol.

Koh WL, Tay YK, Koh MJA. Danazol-induced Stevens–Johnson syndrome in a patient with systemic lupus erythematosus. *Dermatol Online J*. 2015;21(1):17. Permalink http://escholarship.org/uc/item/24v513b9

ASENAPINE-INDUCED MYASTHENIC SYNDROME

A 75-year-old male with a history of bipolar disorder and a depressive episode was managed long-term with lithium 600 mg daily and venlafaxine XR 225 mg daily. Because the patient continued to experience mood symptoms, asenapine (*Saphris*) 5 mg twice daily sublingually was initiated. The patient experienced an improvement in his depressive symptoms; however, after 6 weeks of adjunctive asenapine, the patient experienced distressing adverse effects. The patient developed sudden and progressive dysphonia, facial weakness, and asymmetric palpebral ptosis. The patient's motor symptoms were fluctuating and were progressively worse later in the day. He exhibited hypometric vertical saccades with no diplopia. He had hypomimia and increased tone bilaterally in the upper limbs with normal muscle strength.

Neuroimaging studies excluded brainstem lesions and Parkinson plus syndromes. The patient did not have trauma; renal, thyroid, or electrolyte abnormality; malignancy; or use of corticosteroids or diuretics, which may have impaired his neuromuscular transmission. Acetylcholine receptor (AChR) antibody test results were seronegative. The patient's asenapine was discontinued. Three weeks later, the patient's ptosis, dysphonia, and facial weakness had fully resolved, however his mood symptoms worsened.

The authors summarize that the sudden and progressive development of weakness of extraocular, facial, and laryngeal muscles after the initiation asenapine treatment, associated with marked variability throughout the day, are consistent with the clinical presentation of myasthenic syndrome. The temporal relationship of the onset of myasthenic symptoms and the use of asenapine support asenapine as the possible cause. They also note that this adverse effect has not been noted with this relatively new second-generation antipsychotic and clinicians should be aware of this possible reaction. They advocate that patients receiving asenapine should be closely monitored for unusual symptoms

possibly associated with neuromuscular junction dysfunction.

Hategan A, Bourheois JA. Asenapine-associated myasthenic syndrome. *J Clin Psychopharmacol.* 2015;35(1):107-108.

BLACK HAIRY TONGUE DUE TO LINEZOLID

A 10-year-old male complained of a black discoloration of the dorsum of the tongue for the previous 4 days. The patient had been treated with linezolid (*Zyvox*) 600 mg tablets twice daily for the previous 2 weeks. He received linezolid for a postsurgical infection after surgery for a left-sided radial neck fracture. The patient reported that the blackish pigmentation of the tongue began on the 14th day of linezolid treatment. He was not receiving any concomitant medications with his linezolid therapy. An examination of the patient's oral cavity revealed a black to brown discoloration on the posterior aspect of the dorsal surface of the tongue, with elongated and hypertrophied filiform papillae. A complete blood count was normal. No biopsy results were attainable because the patient's parents would not give consent for a biopsy of the boy's tongue lesion.

The patient was instructed to clean his tongue with normal saline twice daily. After 7 days, the patient's tongue discoloration totally disappeared; after 11 days, the patient's tongue lesion had disappeared. The authors evaluated the adverse reaction by utilizing the Naranjo scale, and it was scored as a probable adverse drug reaction due to linezolid. The authors also reported that a prior case report of black hairy tongue due to linezolid was published in the literature. Petropoulau et al described an association between linezolid with both black hairy tongue and discoloration of the teeth in 3 children. In those cases, the median time to the development of black hairy tongue was also 2 weeks.

Black hairy tongue is characterized by elongation and hypertrophy of filiform papillae of the tongue with brown or black discoloration on the posterior dorsum of the tongue. The condition is self-limiting. Black hairy tongue is usually asymptomatic, with patients sometimes complaining of nausea, halitosis, dysgeusia, or tickling of the tongue. The condition has been associated with smoking, chewing tobacco, poor oral hygiene, xerostomia, substance abuse, use of peroxide-containing mouthwashes, and use of drugs such as steroids, bismuth, methyldopa, tetracycline, olanzapine, and lithium. The exact mechanism behind the development of black hairy tongue is unknown.

The authors want to raise awareness among clinicians about the possibility of this rare adverse effect of linezolid therapy. They recommend that patients should be advised to maintain good oral hygiene to prevent the development of black hairy tongue while receiving linezolid therapy.

Balaji G, Maharani B, Ravichandran V, et al. Linezolid induced black hairy tongue. *Indian J Pharmacol.* 2014;46(6):653-654.

Petropoulou T, Lagona E, Syriopoulou V, et al. Teeth and tongue discoloration after linezolid treatment in children. *Paediatr Infect Dis J.* 2013;23:1284-1285.

ADALIMUMAB-INDUCED PRIAPISM

A 58-year-old Hispanic male with active polyarticular arthritis received a single dose of adalimumab (*Humira*) 40 mg subcutaneously; approximately 10 hours after he received his dose, he developed a painless persistent erection. The patient did not report urinary or sexual difficulty. After 4 days, he developed pain in his penis and then sought care at an emergency department. He reported a prior episode of priapism 10 years earlier that was related to an unknown pain medication. His prior episode of priapism dissipated upon discontinuation of the pain medication.

The patient's priapism was initially treated with corporeal irrigation, which failed, followed by 2 intracavernosal phenylephrine injections and an Ebbehøj shunt. The patient then underwent an Al-Ghorab distal penile shunt. The patient's erection subsided 2 weeks after the distal shunt procedure; however his postsurgical progress was complicated by a corporeo-urethral fistula. The patient declined further surgery and was managed with antibiotics and a Foley catheter. In spite of this adverse reaction, the patient reported subjective improvement of his arthritis after his only adalimumab dose. The patient remained impotent and unable to achieve an erection due to the prior penile surgical interventions. Although the cause of the patient's priapism is unclear, the duration of symptoms (17 days) is similar to adalimumab's mean terminal half-life of 2 weeks.

Because the patient's arthritis had a positive response to adalimumab, his active polyarticular arthritis was now treated with monthly intravenous infusions of abatacept. Abatacept therapy caused a normalization of the patient's C-reactive protein and erythrocyte sedimentation rate with a resolution of his synovitis.

The authors reviewed the possible mechanism in which adalimumab could have caused an ischemic

priapism in this patient. Adalimumab is a tumor necrosis factor-alpha (TNFα) inhibitor, and this class of drugs is used frequently in the treatment of rheumatoid arthritis. TNFα-inhibitors, both monoclonal antibodies and circulating TNF fusion proteins, effectively limit the pro-inflammatory effects of TNFα. They state, "Studies suggest pro-inflammatory cytokines (ie, TNFα) contribute to vascular reactivity. Erectile dysfunction patients have elevated TNFα levels, independent of comorbid conditions. TNFα may impair the pro-erectile action of nitric oxide and endothelial-dependent vasorelaxation of the corpora cavernosa. Proposed mechanisms include inflammation promoting endothelial dysfunction, pro-thrombotic state and TNFα upregulation of phosphodiesterase type 5 which causes hydroxylation of cGMP inhibiting the pro-erectile action of nitric oxide." The authors propose that excess TNFα, from active rheumatoid arthritis, may irritate intracavernosal smooth muscle and endothelial cell function; theoretically, TNFα inhibition may then cause excess local nitric oxide production and subsequent priapism.

Kreitenberg AJ, Ortiz EC, Arkfeld DG. Priapism after tumor necrosis factor alpha inhibitor use [published online ahead of print January 13, 2015]. *Clin Rheumatol*. doi: 10.1007/s10067-014-2858-x. ■