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.

PEMETREXED LONG-TERM MAINTENANCE TREATMENT LEADING TO MULTIPLE FINGER AMPUTATION

A 65-year-old African American female, who had been diagnosed with stage 4 adenocarcinoma of the lung with distant pulmonary metastases, had completed 4 cycles of chemotherapy consisting of carboplatin and pemetrexed (*Alimta*), which had resulted in a partial tumor response. The patient was then initiated on a maintenance dose of pemetrexed of 500 mg/m² administered every 3 weeks, which allowed her disease to remain stable.

After the patient had received her 32nd cycle of maintenance pemetrexed, she reported to the emergency room with complaints of intense pain in the digits of her left hand for the previous week. She stated that the pain had started one day after the

32nd pemetrexed cycle and was initially intermittent, lasting a few minutes to a few hours. The pain was most severe in the fourth digit of her left hand. The patient also complained of episodic numbness, swelling, and blanching of all of her fingers. She did not have any systemic symptoms or a history of smoking.

Upon physical examination, the patient's left hand exhibited mild blanching of all fingers and worsening of pain/blanching on exposure to cold water. Laboratory tests were within normal limits and included a complete blood count, metabolic panel, sedimentation rate, C-reactive protein, and antinuclear antibodies. Her lung cancer was also evaluated as stable based on imaging studies. An arterial Doppler ultrasound of her upper extremity revealed a normal macrocirculation. The patient's symptoms were thought

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to be related to Raynaud's phenomenon induced by chemotherapy. She was advised to avoid cold and was prescribed a calcium channel blocker to combat the condition. The patient had 2 additional emergency room visits with the same complaints of intense pain in the fingers of her left hand. An additional battery of tests that included cytoplasmic antineutrophil cytoplasmic antibodies, perinuclear antineutrophil cytoplasmic antibodies, cryoglobulins, C3 and C4 complement, and 2-dimensional echocardiography were all within normal limits.

The patient proceeded to receive her 33rd cycle of maintenance pemetrexed. After pemetrexed was completed, she experienced significant worsening of finger pain and developed swelling and cyanosis of the fingers of her left hand. A black eschar formation was noted on the tip of the patient's left fourth digit. The patient was evaluated with an emergency angiogram of the left upper extremity, which revealed poor perfusion in the distal digital arteries with the poorest perfusion in her fourth digit. The patient did not have any evidence of a thrombus, embolus, or any focal area of stenosis. A D-dimer test was within normal range and was similar to the patient's baseline level prior to the initiation of chemotherapy.

Based on the extent of the patient's occlusion and gangrene formation, her fourth digit was amputated. Her pemetrexed infusions were discontinued since pemetrexed-induced endothelial dysfunction was suspected. Two months later, the patient needed amputation of the left third digit due to ischemia/gangrene. The patient has not experienced additional episodes of digital ischemia or gangrene over 21 months of follow-up. While she was not receiving pemetrexed, the patient's lung cancer progressed after 10 months; she was initiated on daily erlotinib treatment and her cancer has since stabilized.

The authors drew the following conclusions based on the patient's case. First, pemetrexed-induced nonembolic occlusive arterial disease can mimic Raynaud's phenomenon in the initial stages. Second, patients on maintenance pemetrexed chemotherapy who report persistent digital pain require special attention and thorough investigation. Third, the time window from the beginning of pain to the development of a nonsalvageable gangrenous digit may be short. Fourth, cumulative toxicity from multiple pemetrexed infusion cycles may lead to severe endothelial dysfunction and limb-threatening gangrene. Fifth, the potential risk of long-term

pemetrexed use should be discussed with patients who have a high predisposition for impaired micro- or macrocirculation. Sixth, postmarketing surveillance of long-term pemetrexed (>30 cycles) use should be studied to determine a definitive causal relationship between prolonged pemetrexed use and peripheral arterial ischemic occlusion.

Gupta N, Gupta S, Gandhi S, et al. Critical acral ischemia leading to multiple finger amputation: Side effect of long-term (>30 cycles) pemetrexed maintenance treatment in a patient. *Br J Clin Pharmacol*. 2014;78(5):1167-1168.

CARDIOVASCULAR COMPLICATIONS AFTER ENERGY DRINK CONSUMPTION

Goldfarb et al performed a systematic review of all published cases of acute cardiovascular events potentially associated with energy drink consumption. They restricted their results to reports that contained sufficient clinical information and cardiac investigations. The authors extracted available data with regard to patient age, gender, type of cardiovascular event, brand of energy drink consumed, estimated dose of caffeine ingested within 24 hours of the cardiovascular event, co-ingestion with alcohol or other substances, pre-existing cardiovascular disease, and the results of cardiovascular investigations. The authors classified an estimated ingestion of 480 mg or more of caffeine within 8 hours as "acute heavy consumption"; this corresponds to drinking more than 3 cans or bottles of several popular energy drinks in a short period of time. Heavy chronic consumption was characterized as 200 mg or more per day of caffeine from energy drinks over 1 week. The authors defined serious cardiovascular events as cardiac arrest, ventricular arrhythmia, or ST-segment elevation.

The authors evaluated a case series of 17 cases of energy drink-induced cardiovascular events that met their search criteria. They point out that their search results are prone to publication bias in that the majority of affected cases involved teenagers and young adults, which represent the largest demographic of energy drink consumers. They could not conclude that any one specific additive or brand of energy drink was more likely to cause adverse cardiovascular effects.

The authors did find that heavy consumption of energy drinks was implicated in at least 7 cases, and 5 cases were associated with co-ingestion of alcohol or other drugs. Of note, in all 5 reported cases of ST-elevation, the presenting symptom was severe chest pain. They also noted that 11 cases presented with serious adverse events, including cardiac arrest.

Of these serious cases, the majority occurred either with acute heavy consumption of energy drinks or consumption in combination with alcohol or other drugs. In at least 2 of these cases, energy drinks may have unmasked an underlying cardiac channelopathy that predisposed the patient to ventricular arrhythmia. In the remaining cases, no predisposing cardiac abnormality was found to explain the cardiovascular event.

The authors list a number of reasons that energy drinks may predispose patients to acute adverse cardiovascular events. First, caffeine in doses that might be consumed in an energy drink (250 mg) has been shown in normal subjects to increase levels of circulating catecholamines. Because energy drinks are often consumed in an excessive or rapid manner, this may lead to a dangerous surge in catecholamines. Second, there may be additional sources of caffeine in many energy drinks. Energy drinks may contain common additives that contain substantial amounts of caffeine, such as guarana, kola nut, and yerba mate. Several brands do not disclose on their labels the total caffeine content in their product. Third, energy drinks have been shown to increase platelet aggregation and worsen endothelial function, reduce myocardial blood flow when consumed before exercise, and significantly increase myocardial oxygen demand in experimental models. All of these effects could result in cardiac ischemia. Fourth, caffeine can cause hypokalemia in a dose-dependent manner, which could contribute to the occurrence of ventricular arrhythmias and sudden death.

In reviewing their findings, the authors acknowledge that the large number of consumers and the few reported events suggest that the risk related to energy drinks may, in fact, be small. However, because such adverse events are likely to be severely underreported, additional epidemiologic research is required to accurately estimate the magnitude of risks related to energy drink consumption, identify vulnerable populations, and assess important interactions with additives in energy drinks, alcohol, and other co-ingestions.

The authors advise that caution is warranted when consuming energy drinks (and young adult, youth, or caffeine-naïve populations should consider avoiding them altogether), especially in large quantities over short periods of time or mixed with alcohol or other drugs. They also recommend that energy drink product labeling should be improved to include the total caffeine content from all sources (including natural sources).

Goldfarb M, Tellier C, Thanassoulis G. Review of published cases of adverse cardiovascular events after ingestion of energy drinks. *Am J Cardiol.* 2014;113:168-172.

COMPARTMENT SYNDROME DUE TO EXTRAVASATION OF INTRAVENOUS CONTRAST

A 60-year-old male patient who was being evaluated for chest pain and shortness of breath was scheduled to receive a thoracic CT scan with contrast to detect a possible pulmonary embolism. The patient received 100 mL of iohexol (*Omnipaque*) at a rate of 1.5 mL/s into the dorsum of the right hand. At the start of the injection, the patient experienced minimal pain in the hand but did not notify the personnel responsible for the test. Twenty minutes after the CT scan, the patient noticed swelling and severe pain on the back of his hand. Upon examination, the hand was pale, tense, and swollen, with blisters on the back and loss of sensation. Capillary refill time was increased in the hand; the patient was unable to move his fingers and any attempt to do so was extremely painful. A large well-demarcated ecchymosis appeared on the back side of his hand as well as continued marked edema. A radiograph revealed a significant accumulation of contrast within the extravascular space. Conservative measures (ice, elevation of the forearm, intravenous administration of corticosteroids and analgesic treatment) did not improve the patient's symptoms.

The patient was diagnosed with compartment syndrome, and an urgent dorsal fasciotomy was performed within 2 hours after extravasation of the contrast agent. A fasciotomy is a surgical procedure in which the fascia is cut to relieve tension or pressure and is commonly used to treat the resulting loss of circulation to an area of tissue or muscle. Compartment syndrome is a complex of symptoms caused by increasing pressure of soft tissues within a confined space that threatens blood circulation and the functions of the structures found within that space.

Immediate relief occurred after the fasciotomy incision, and the color and consistency of the patient's hand improved and turned to a pinkish hue. On the day of surgery, the swelling was decreased dramatically and supple range of motion of the fingers was noted. On day 3, radiographs of the hand became gradually clearer; on the fourth day, the fasciotomy was closed without the need for skin grafting. Twenty-one days after surgery, the patient had fully recovered hand function.

The authors point out that the main reasons involved in the increase of accidental extravasation

of contrast volumes exceeding 50 mL are the use of rapid infusion pumps and the increase in the use of CT scans in monitoring cancer patients. Patient factors to consider when assessing the risk of extravasation are arterial or venous insufficiency, poor lymphatic drainage, low muscle mass, and subcutaneous tissue atrophy. They recommend that the risk of extravasation can be reduced by the use of nonionic contrasts of lower osmolality, which produce less direct tissue damage than ionic contrasts of higher osmolality. Direct supervision of infusion pumps or the use of devices that detect early extravasation through impedance can be useful. Use of the larger veins at the antecubital fossa is a recommended site for intravenous access, and an appropriate catheter gauge should be considered to withstand infusion volume and speed.

Yurdakul E, Salt O, Durukan P, et al. Compartment syndrome due to extravasation of contrast material: A case report. *Am J Emerg Med.* 2014;32:115e3-115e5.

BLUE-GRAY MUCOCUTANEOUS DISCOLORATION WITH EZOGABINE

The authors report 2 cases of blue-gray mucocutaneous discoloration associated with the chronic use of ezogabine (*Potiga*). The first case occurred in a woman in her 30s with light skin (phototype II). The Fitzpatrick Scale is a method to classify the response of different types of skin to ultraviolet (UV) light. The scale ranges from I to VI, with class I always burning from the sun and class VI tanning easily and never burning. The patient was classified as Fitzpatrick Scale class II; she has fair skin that easily burns and tans poorly with sun exposure. She presented with a blue-gray discoloration of the skin. She had begun to notice changes in her complexion several years previously. The patient has a history of pharmacoresistent temporal lobe epilepsy with primary generalized tonic-clonic seizures. Her medication history revealed that she had received the following medications for the past 6 years: valproic acid, gabapentin, oxcarbazepine, and ezogabine 350 mg 3 times daily.

The patient's affected skin appeared blue-gray and slightly hyperpigmented; the discoloration was most pronounced on the sun-exposed areas of the face and lips. Examination of the mouth revealed blue pigmentation of the hard palate. In addition, 2 blue macules were noted around the knees, and the patient's toenails and fingernails showed transverse blue-colored bands. Ophthalmologic examination revealed black pigment deposits on the palpebral conjunctivae and lower fornices, however the cornea and fundi appeared uninvolved.

A complete metabolic work-up and a variety of tests to evaluate possible causes for the skin discoloration were all negative. Since mucocutaneous dyspigmentation can be induced by a wide variety of genetic, metabolic, and endocrine diseases as well as deposits of metal ions, all of these potential causes were excluded by both medical history and extensive laboratory investigation. The patient was advised to discontinue ezogabine. Four months after discontinuation, a significant improvement of the patient's skin, oral mucosa, and nail dyspigmentation were noted.

A second patient in her 30s with skin phototype II was seen. The dyspigmentation in this patient had been present for 2 years. She had received treatment for approximately 6 years for generalized epilepsy, predominantly manifesting as absence seizures, with multiple antiepileptic medications including carbamazepine, levetiracetam, clobazam, and ezogabine 300 mg 3 times daily. The patient exhibited a blue-gray mucocutaneous dyspigmentation localized to the face, including the lips. Her fingernails showed transverse blue-colored bands. Further examination disclosed blue pigmentation of the hard palate and black-pigmented deposits on the palpebral conjunctivae and lower fornices, with no involvement of other compartments of the eye. The patient was advised to discontinue treatment with ezogabine, but she refused and the condition remained as she presented.

The authors point out that the pathogenesis for drugs to cause dyspigmentation can vary. Generally, dyspigmentation results from the accumulation of melanin either free in the dermis or contained within cells, particularly the dermal macrophages, rather than the basal layer of the epidermis. The accumulation of melanin may be due to its hyperproduction by the epidermal melanocytes specifically stimulated by the medication or it may represent a nonspecific cutaneous inflammatory reaction to the drug. Alternatively, a stable drug-melanin complex may prevent melanin clearance in the dermal macrophages. This mechanism is often exacerbated by sun exposure, leading to accentuation of the lesions in sun-exposed areas. Other reported mechanisms are accumulation of the triggering drug without melanin; synthesis of special pigments, such as lipofuscin, under the direct influence of the drug; or deposition of iron owing to the drug-induced damage to dermal vessels.

The authors point out that the patient's peculiar skin pigmentation could be explained by the Tyndall effect, which is the perception of dermal melanin as blue, gray, or blue-gray because of the selective scatter of short wavelengths. It is unknown whether

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used in the hospital setting. Based on current evidence, routine use of subcutaneous ketorolac cannot be recommended for use as intermittent bolus doses but appears to be a safe option when no other route of administration is available. Ketorolac CSI may be considered when patients have been unresponsive to other pain modalities.

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ezogabine induces melanin synthesis or, alternatively, hampers the degradation of melanin. Nuclear magnetic resonance imaging and mass spectrometry results provided no evidence of drug deposition in the tissue. However the authors state that they cannot rule out the presence of drug derivatives or metabolites that could not be detected by their analysis.

The US Food and Drug Administration has since published a statement announcing that ezogabine can cause blue skin discoloration and pigment changes in the retina. In evaluating 605 patients, 6.3% were found to have skin discoloration. At this time, all the patients had not been analyzed, so the rate may be an underestimation. One-third of patients given eye examinations had retinal pigment changes. It is

not known whether the pigment is deposited in other organs as well or whether the changes are reversible.

The authors state that the mainstay of treatment for drug-induced dyspigmentation is sun avoidance with application of sunscreen and, if possible, interruption of the implicated drug. In most cases, these measures lead to improvement; however, it may be slow improvement. The significant improvement in the mucocutaneous dyspigmentation following discontinuation of ezogabine, as observed in the first patient, suggests that ezogabine-induced dyspigmentation might be reversible.

Shkolnick TG, Feuerman H, Didkovsky E, et al. Blue-gray mucocutaneous discoloration: A new adverse effect of ezogabine. *JAMA Derm*. 2014; 150(9):984-989. ■