ISMP Adverse Drug Reactions

Furosemide-Induced Immune Thrombocytopenia

Type I Interferon-Induced Ischemic Colitis

Dronedarone-Associated Acute Renal Failure

Modafinil-Induced Psychosis

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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.

FUROSEMIDE-INDUCED IMMUNE THROMBOCYTOPENIA

The authors present a case of persistent thrombocytopenia that has been occurring in a patient for 7 years and was not attributed to furosemide administration. An 84-year-old Caucasian man came to an emergency room complaining of back pain and was admitted and diagnosed with a urinary tract infection. The patient had a long history of congestive heart failure (CHF) for which furosemide had been initiated 7 years earlier. The patient's oral furosemide dose ranged from 40 to 160 mg/day during this time frame. The patient's medication history prior to admission consisted of simvastatin, potassium chloride, chlorthalidone, ramipril, and a multivitamin. On admission, the patient's chlorthalidone and ramipril were discontinued.

The patient's medical history also included coronary artery disease, hypertension, type 2 diabetes mellitus, cryptogenic cirrhosis, and "idiopathic" immune

thrombocytopenia for the past 7 years. The patient's diagnosis of thrombocytopenia coincided with his CHF diagnosis and the initiation of furosemide therapy. His chronic thrombocytopenia had caused multiple superficial purpuras, and he had received at least one platelet transfusion.

During the patient's current hospital stay, his CHF had become decompensated and he required high doses of intravenous furosemide for diuresis. At the start of the patient's intravenous furosemide, his platelet count was $119 \times 10^3/\text{mm}^3$ and rapidly dropped to $36 \times 10^3/\text{mm}^3$. The authors investigated inpatient and outpatient medical records evaluating prior platelet counts and the doses of furosemide administered. They uncovered a similar relationship when oral and intravenous formulations had been administered over the previous 7 years. A dose increase from 80 mg/day to 160 mg/day resulted in a platelet count drop from $143 \times 10^3/\text{mm}^3$ to $89 \times 10^3/\text{mm}^3$. After a dosage reduction back to 80 mg/day,

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the patient's platelet count returned to $144 \times 10^3/\text{mm}^3$. This relationship between thrombocytopenia and furosemide was discovered on day 9 of the patient's hospital stay, at which time furosemide was discontinued and torsemide was initiated. Furosemide was added to the patient's allergy profile, which previously reflected no known drug allergies. The discontinuation of furosemide was followed by a resolution of thrombocytopenia and an increase in platelet count to $168 \times 10^3/\text{mm}^3$, which was a level that the patient had not achieved during 7 years of furosemide therapy.

Although furosemide was the likely culprit for the patient's thrombocytopenia, an evaluation of the medications the patient had received during his hospital stay was warranted. The patient had received levofloxacin and later vancomycin during his admission. There was no influence on the timing of the initiation and discontinuation of these drugs on the observed trending of platelet counts.

The authors report that during a later hospital admission for decompensated CHF, the patient received a one-time dose of furosemide 40 mg and his platelet count dropped from an admission platelet count of $206 \times 10^3/\text{mm}^3$ to $96 \times 10^3/\text{mm}^3$. A year after the discontinuation of furosemide, the patient's platelet counts continued to be within normal limits with a maximum platelet count of $206 \times 10^3/\text{mm}^3$, which was the highest platelet count he had attained in the previous 9 years.

The authors point out that the identification of drug-related thrombocytopenia can be discovered by a review of medical records. Many drugs in addition to the commonly known gold salts and quinine can potentially cause drug-induced immune thrombocytopenia. A more definitive diagnosis of drug-induced thrombocytopenia can be made with whole platelet assays, such as glycoprotein-specific immunochemical techniques. These techniques were not utilized by the authors in this case. The confounding factor in this patient was that he was noted to have cryptogenic cirrhosis, which was thought for many years to be the cause of his thrombocytopenia.

The authors noted that the patient's thrombocytopenia demonstrated dose-dependent and route-dependent responses pointing to the rarer, drug-dependent induction of antibodies. This fact along with the influence of cirrhosis may explain why the patient's platelet count never increased to levels observed before starting furosemide. According to postmarketing studies, 2.4% of patients receiving furosemide have experienced thrombocytopenia.

Considering the frequency of furosemide use, the cumulative total number of patients who could potentially experience thrombocytopenia is substantial. In closing, the authors warn that an increased awareness of drug-induced immune thrombocytopenia is needed, along with increased scrutiny of drugs as a potential cause.

Ochoa PA, Fisher T. A 7-year case of furosemide-induced immune thrombocytopenia. *Pharmacotherapy*. 2013;33(7):e162-e165.

TYPE I INTERFERON-INDUCED ISCHEMIC COLITIS

A rigorous review was conducted to determine a possible association between type I interferons and the development of ischemic colitis. The authors evaluated reports derived from the US Food and Drug Administration (FDA) Adverse Event Reporting System (AERS) as well as published reports.

There are 11 type I interferon products available, IFN- α -2a (*Roferon A*), IFN- α -2b (*Intron A*), IFN- α -n3 (*Alferon N*), peginterferon alfa-2b (*PegIntron*), interferon alfacon-1 (*Infergen*), peginterferon alfa-2a (*Pegasys*), peginterferon alfa-2a and ribavirin (*Peginterferon*), IFN- β -1a (*Avonex*, *Rebif*), and IFN- β -1b (*Betaseron*, *Extavia*). Type I interferons are structurally related, share a common receptor (type I interferon receptor), and play an important role in immunity and autoimmunity. Specifically, type I interferons initiate cellular reactions that result in a host-protective antiviral response. INF- α is approved by the FDA for treatment of hepatitis C virus (HCV) and INF- β is approved for the treatment of multiple sclerosis.

Ischemic colitis is not a known adverse effect of all type I interferons, whereas hypotension is an adverse effect that is a common cause of ischemic colitis. Ischemic colitis results from a decrease in blood flow to the colon, which causes inflammation. Symptoms of ischemic colitis are abdominal pain, diarrhea, and hematochezia. Almost 50 drugs and drug classes have been associated with ischemic colitis.

The evaluation of ischemic colitis cases derived from AERS in patients receiving IFN- α revealed that the majority of the cases were in males (65%). Most patients were between the ages of 50 and 70 years of age, with a recovery rate of 70.6%. A literature review of ischemic colitis case reports in patients receiving IFN- α found the majority of reported cases in males older than 50 years. The evaluation of ischemic colitis cases derived from AERS in patients receiving IFN- β revealed that all probable cases occurred in females

between the ages of 50 to 70 years, with a recovery rate of 74.4%. There were no published case reports of IFN- β -induced ischemic colitis in the literature.

The authors summarize, “the median age was similar in patients receiving IFN- α and IFN- β who developed ischemic colitis. All of the IFN- β cases were in females while 35% of IFN- α cases were in females. The rate of recovery from ischemic colitis was similar in IFN- α and IFN- β patients.” In evaluating their results, the authors point out that sex differences noted in their results are explainable. Hepatitis C infection is equally common in males and females; however, females have a lower probability of disease progression. In light of this, women with HCV have a tendency to defer treatment or take medications that are less potent than interferons compared to males. These reasons could account for the fact that their study presented almost twice as many cases reported in men compared to women developing ischemic colitis after receiving IFN- α for HCV. Conversely, ischemic colitis occurring in patients treated with IFN- β was more common in females. This is consistent with an overall female predominance in multiple sclerosis seen in clinical epidemiology studies. Because exogenous estrogen use is also a risk factor for ischemic colitis, the risk for ischemic colitis may be further accentuated in females.

The authors conclude that HCV and multiple sclerosis have other treatment options that do not include interferons. Clinicians treating patients with heart disease, diabetes, and other conditions associated with ischemic colitis should take into account the adverse effects of interferons versus alternative therapy. Their study does not prove causality but instead suggests a correlation that complements existing published literature on the topic of ischemic colitis.

Salk A, Stobaugh DJ, Deepak P, et al. Ischemic colitis with type I interferons used in the treatment of hepatitis C and multiple sclerosis: An evaluation from the Food and Drug Administration adverse event reporting system and review of the literature. *Ann Pharmacother*. 2013;47:537-542.

DRONEDARONE-ASSOCIATED ACUTE RENAL FAILURE

Dronedaronone (*Multaq*) is an antiarrhythmic agent that is a multichannel blocker derivative of amiodarone. It is already known that dronedaronone partially inhibits the tubular transport of creatinine, with a slight increase in creatinine concentrations leading to a limited rise in serum creatinine not correlated with a decline in renal function. In the PALLAS study,¹ which was prematurely terminated, adverse

drug reactions related to renal function, including serious renal failure, were more frequently reported in the dronedaronone group compared to the placebo group. In 2009, 4 cases of dronedaronone-associated acute kidney failure were collected in MEDWATCH.

The authors queried the Italian Medicines Agency (AIFA) pharmacovigilance database for all suspected adverse reactions related to dronedaronone use. The quality of data collected in the database is ensured, because each report is verified by both the respective pharmacovigilance center and the AIFA. Dronedaronone queries revealed 4 cases of acute renal failure (ARF), 2 cases of renal failure (RF), and 3 increases in blood creatinine. Six of the 9 cases occurred in females, and patients ranged from 61 to 84 years of age. The majority of the cases occurred within the first 13 days of initiation of dronedaronone therapy, with a range of 6 days to 2 months. Except for 1 case, all reports of renal failure required hospitalization or resulted in prolonged hospitalization. In 7 cases, the only suspected drug was dronedaronone. In all except 1 case, a positive dechallenge was reported.

Although only 9 cases were reported, the authors caution that this is not a negligible number when compared with the initial low use of dronedaronone in Italy. Several studies have shown that for each serious case that is reported, more than 15 are not reported. Based on this, the authors suspect that more than 100 cases of renal disorders could have occurred during this time period.

The patients were older men and women with several concomitant conditions; the authors state that it is possible that these conditions may have precipitated renal failure. The authors note that these cases are an important signal that periodic evaluation of renal function should be conducted in patients treated with dronedaronone. The authors also point out that their findings add to the body of evidence concerning cardiovascular, hepatic, and pulmonary risks, and they suggest the need to reconsider the risk:benefit ratio of dronedaronone. Clinicians should be aware of the risks of dronedaronone use and screen patients appropriately for ARF risk factors before starting dronedaronone therapy.

Biagi C, Venegoni M, Melis M, et al. Dronedaronone-associated acute renal failure: Evidence coming from the Italian spontaneous ADR reporting database. *Br J Clin Pharmacol*. 2013;75(5):1351-1355.

MODAFINIL-INDUCED PSYCHOSIS

A 21-year-old male presented to the authors' psychiatric facility for a second opinion. The patient

had a family history of depression and was preparing for higher education after completing 12th grade in India. The patient had a 3-week history of schizophrenic symptoms such as somatic passivity, delusions of reference, and auditory, visual, and olfactory hallucinations. The patient had a history of interrupted use of modafinil (*Provigil*) for the previous 2 years and a gradual increase in dosage from 400 mg daily to 1,600 mg daily over a period of 16 months.

The patient had started to use modafinil without a prescription 2 years ago for a period of 4 months to improve his concentration during his preparation to take an academic entrance examination. The patient had not experienced any adverse effects over 16 months. After this period of time, the patient stopped using modafinil for a 1-month period because he was not involved in examination preparation. However when the patient restarted his modafinil, his dose rapidly went up to 1,600 mg daily within 1 week and continued at the same dose for the next 5 to 6 days. While taking a dose of 1,600 mg daily, he started complaining that the girls in the next room to his were calling him by name and spraying chloroform into his room that made him unconscious and that they would come into his room and fondle and sexually abuse him. These experiences continued for the next 7 days after which he decreased the dosage of modafinil to 800 mg daily for the next 4 days and then discontinued.

Upon discontinuation, a significant improvement in his symptoms occurred within the same week. After this time, modafinil was not restarted, and there were no further reports of his earlier symptoms. The patient consulted a psychiatrist and was treated with risperidone 4 mg daily and fluoxetine 20 mg daily for a period of 2 weeks. The patient developed akathisia with risperidone; it was discontinued, and quetiapine 50 mg daily was initiated. After a 1-week inpatient stay for evaluation, quetiapine was tapered and stopped, and the patient was discharged without any medications. He was advised to have regular follow-up.

During a telephone follow-up 7 months later, the patient reported that he had been admitted to a medical

graduate program. He continued to complain about his lack of concentration in his studies and consulted a local psychiatrist for possible methylphenidate to improve concentration. He was denied a methylphenidate prescription and restarted modafinil without a prescription at a dose of 600 mg daily for approximately 12 days. The patient reported an absence of his previous psychotic symptoms, and he had an improvement in concentration. After repeated consultation with a local psychiatrist, atomoxetine 50 mg daily was prescribed for reduced concentration with no improvement. Further evaluation at the authors' faculty was advised, but the patient was then lost to follow-up.

The authors summarize that this case reveals a strong temporal relationship between administration of high doses of modafinil, despite the use of it for quite a long time in a lower dose, and the appearance of schizophrenic-like psychotic symptoms. The disappearance of frank schizophrenic symptoms with stoppage of modafinil suggests that psychotic symptoms are induced by high-dose modafinil. Modafinil is a novel wake-promoting agent with a complex profile of neurochemical and behavioral effects distinct from those of amphetamine. Modafinil has a wide variety of off-label indications in psychiatry, including the treatment of negative symptoms of schizophrenia. Clinicians should be aware that modafinil may induce psychosis with positive symptoms when used to manage negative symptoms of schizophrenia. The authors state that clinicians should have a high index of suspicion when patients demand attention-enhancing drugs and screen for prodrome of psychosis.

Rudhran V, Manjunatha N, John JP. High-dose, self-administered modafinil-related psychosis. Is it the pedal to the prodrome of psychosis? *J Clin Psychopharmacol*. 2013;33(4):576-577.

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