ISMP Adverse Drug Reactions

Telaprevir-Related Dermatitis

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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.

TELAPREVIR-RELATED DERMATITIS

A study was undertaken to evaluate the incidence, type, and severity of telaprevir-associated skin reactions. Skin manifestations have previously been reported in association with pegylated interferon and ribavirin treatment of hepatitis C virus (HCV). Up to 30% of patients experience a usually pruritic dermatitis or eczematiform skin eruption. The eruptions are most often mild or moderate and seldom lead to the discontinuation of treatment. When the HCV protease inhibitor telaprevir is added to pegylated interferon and ribavirin therapy, it significantly increases the rate of sustained viral response in patients with genotype 1 chronic HCV infection.

The authors, who were dermatologists, reviewed data from phase 1 to 3 studies of telaprevir in combination with interferon and ribavirin, which included a total of 2,290 patients. The authors assessed available information including photographs, biopsy results, and clinical summaries of all cases with skin eruptions reported as moderate or severe during the telaprevir clinical development program. In their review, adverse skin events occurred significantly more frequently with telaprevir plus peginterferon and ribavirin (56%) as compared to placebo plus peginterferon and ribavirin (34%). In addition, severe skin reactions were more frequent in telaprevir-treated patients (3.7% vs 0.4%), as was discontinuation of

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telaprevir or placebo because of skin complaints (6.4% vs 0.4%).

Approximately 5% of patients treated with telaprevir developed extensive skin eruptions that are infrequent with peginterferon and ribavirin alone. The addition of telaprevir increases the incidence and the severity but does not change the nature of the eruption most commonly observed with peginterferon and ribavirin. Cases of severe cutaneous adverse reactions were observed, including 3 suspected cases of Stevens Johnson Syndrome (SJS) and 11 suspected cases of drug rash with eosinophilia and systemic symptoms (DRESS). Five cases of severe cutaneous adverse reactions, 2 SJS and 3 DRESS, were assessed as likely being caused by telaprevir therapy. Nearly one-fourth of cases of cutaneous reactions began within 4 days and 46% began after 4 weeks of telaprevir therapy.

Telaprevir-related dermatitis occurs in a majority of telaprevir-treated patients. The authors state that in clinical practice, telaprevir-related dermatitis is most often of limited extent. On the basis of their findings, the authors suggest that clinicians focus on the following 2 objectives: “(1) vigilance for early signs of severe cutaneous adverse reactions (SCAR) that would require immediate discontinuation of all treatment and (2) therapy to alleviate signs and symptoms of telaprevir-related dermatitis to help patients tolerate treatment.” No controlled study is available on the optimal management of telaprevir-related dermatitis. However, the treatments for contact dermatitis or atopic dermatitis may help control the symptoms.

Roujeai JC, Mockenhaupt M, Tahan SR, et al. Telaprevir-related dermatitis. *JAMA Dermatol.* 2013;149(2):152-158.

NEUROLEPTIC MALIGNANT SYNDROME WITH RISPERIDONE LONG-ACTING INJECTION

A 50-year-old man with a 21-year history of chronic schizophrenia was admitted to the hospital because of medication noncompliance. He had been treated perviously with various oral antipsychotics including haloperidol without marked extrapyramidal adverse effects or discernible neuroleptic malignant syndrome (NMS). Due to his poor medication adherence, risperidone long-acting injection (RLAI) was prescribed. He initially received oral risperidone, 3 mg/day, for 7 days before RLAI 25 mg was added. Two weeks later, the second dose of RLAI was increased to 37.5 mg and was continued every 2 weeks thereafter. Oral risperidone was discontinued 5 weeks after RLAI initiation. The patient also received oral levomepromazine 30 mg daily, trazodone 50 mg daily, and flunitrazepam 2 mg daily for insomnia. The patient

received RLAI on 4 occasions and was discharged after 7 weeks to the home-visit nursing service.

Ten days after discharge, the patient complained of difficulty swallowing, and extrapyramidal adverse effects were suspected. However, RLAI was continued. His dysphagia continued to worsen, and 9 weeks after discharge he was readmitted with the home-visit nurse's help because he showed diaphoresis and was immobile and mute.

On admission, he had rigidity, tremors, dysphagia, tachycardia (107 bpm), diaphoresis, urinary incontinence, and delirium but no fever. Laboratory tests revealed leukocytosis (12,500 cells/m³) and increased creatine phosphokinase (CPK 1,089 IU/L). There were no abnormalities on CT scan of the brain, EEG, chest x-ray, or EKG. On hospital day 3, he developed a fever of 37.8°C and marked rigidity and tremors. On hospital day 4, the rigidity worsened, the patient had trouble opening his mouth, and the CPK increased to 1,387 IU/L. The decision was made to administer intravenous dantrolene 40 mg daily. Starting the next day through hospital day 8, the patient's CPK slowly returned to normal and NMS resolved; dantrolene was discontinued at that time.

After 7 weeks in the hospital and 8 weeks since the last RLAI dose, olanzapine 5 mg was initiated and was gradually increased to 10 mg daily. The patient was discharged and has not experienced an NMS relapse in the 11 months since his discharge.

The authors concluded that, “The patient developed NMS during treatment with RLAI and levomepromazine. There are currently no cases of low-dose levomepromazine alone causing NMS although there have been cases in which low-dose risperidone has induced NMS. Whereas it cannot be completely excluded that polypharmacy was associated with NMS in this patient, RLAI is thought to have been the main contributor to NMS onset.”

The authors tracked the patient's risperidone blood levels and the severity of his NMS symptoms. At present, there is no consensus on the relationship between NMS and serum antipsychotic levels. NMS in the patient improved, although the serum concentration of risperidone active moiety kept rising, and then NMS disappeared despite a steady state serum concentration. The dantrolene might have interrupted the progression of NMS and improved the patient's condition. This case supports the use of standard NMS treatment protocols in the treatment of risperidone-induced NMS.

Yamashita T, Fujii Y, Misawa F. Neuroleptic malignant syndrome associated with risperidone long-acting injection. A case report. *J Clin Psychopharmacol.* 2013;33(1):127-129.

TIGECYCLINE-RELATED PANCREATITIS

A retrospective cohort study was conducted to review spontaneous reports of pancreatitis related to tigecycline use in the US Food and Drug Administration (FDA) Adverse Event Reporting System (AERS). Their goal was to identify any clinically relevant characteristics that might be useful in identifying patients at risk of pancreatitis with the use of tigecycline.

Pancreatitis is a known adverse effect of tetracyclines, but it was not originally detected with tigecycline during the FDA approval process. Sixty-two cases of pancreatitis associated with tigecycline use were reviewed. Patient demographics, duration of tigecycline therapy, time to onset of pancreatitis, and clinical outcome were examined.

The authors report that pancreatitis was more common in women and the average duration of tigecycline use before the onset of pancreatitis symptoms was 12.5 days. These findings are similar to previously published findings. Four patient deaths were reported; three of the patients were women weighing less than 100 pounds and 2 of the women were 65 years old. Three of the women were receiving tigecycline for sepsis or pneumonia, and the duration of tigecycline use before onset of pancreatitis was 7 days in each patient. The exact mechanism by which tigecycline causes pancreatitis is unknown. The 3 most common hypotheses are high biliary concentration, hypertriglyceridemia, and formation of a toxic metabolite.

One limitation of the study is that many AERS reports lack sufficient case detail to ensure that all cases meet the definition of drug-induced pancreatitis. Second, the variables analyzed are limited to those provided by the AERS database. Important variables such as comorbidities, race-ethnicity, and laboratory values were not available for analysis. Third, the results cannot be generalized to the population as a whole, because it is not possible to calculate an incidence of tigecycline-induced pancreatitis based on the data provided in the AERS database.

Okon E, Engell C, Manen RV, et al. Tigecycline-related pancreatitis: a review of spontaneous adverse event reports. *Pharmacotherapy*. 2013;33(1):63-68.

VENLAFAXINE-RELATED PSYCHOSIS

A 48-year-old man with a history of major depression, anxiety, benzodiazepine, and amphetamine dependence was transported to the hospital by police due to severe delusional thoughts and erratic behavior. The patient incorrectly believed that his ex-wife and 2 children had been killed in a car accident due to his ex-wife's negligence. In reality, this event had not

occurred. The patient had been running between 2 apartment buildings and banging on doors and yelling for people to call 911. Upon arrival at the emergency department, he was given lorazepam and olanzapine. The patient was restless, moving randomly, picking at what he perceived to be objects, and talking to himself. The patient's speech was not slurred, but he continued to have visual hallucinations and delusional thoughts.

The medications the patient received at home were venlafaxine sustained action (SA) 300 mg daily, bupropion SA 150 mg daily, hydroxyzine 10 mg 3 times daily as needed and 20 mg at bedtime, clonazepam 2 mg daily, and metoprolol tartrate 50 mg twice daily. Upon admission, bupropion and hydroxyzine were discontinued, metoprolol was held for 6 days, and the venlafaxine SA dosage was reduced to 225 mg daily.

On day 2 of his hospital stay, his delusional thoughts had resolved and he was able to give a clear history. He reported he had not been taking his prescribed medications as directed. The patient related an account of his medication misadventure. He stated that he had "tapered and discontinued his clonazepam three weeks before admission and he had self-increased his bupropion to 300 mg daily for anxiety and depression and therefore he had run out of bupropion approximately two weeks prior to admission." He also stated that he "had increased his venlafaxine SA to 450 mg daily." After 1 week, the patient related an account of "experiencing auditory hallucinations (AH) of songs coming from under his bed and hearing voices reporting a crime on a radio station although the radio was not on." At this time, he increased his venlafaxine SA dosage to 600 mg daily for an additional week. The patient then began having "visual perceptual disturbances of his knees and boxes melting, other objects evaporating and drops of water dripping from the ceiling." He was admitted approximately 2 days later.

By day 4 of the admission, he was no longer having visual hallucinations; by day 5, his AH had resolved and he was discharged 9 days after admission. The authors evaluated the potential causes of the patient's admission. Venlafaxine is a serotonin norepinephrine reuptake inhibitor, a weak inhibitor of dopamine reuptake, and a substrate for P-glycoprotein. A more pronounced norepinephrine reuptake inhibition is noted at higher doses. The authors postulate that the patient's psychosis was possibly due to the dopamine effects of venlafaxine, because the patient was taking a very high dose of venlafaxine prior to admission (600 mg daily). In reviewing other potential causes of the patient's psychosis, it is noted that the last use of a stimulant was more than a month prior to admission;

he had stopped his clonazepam 3 weeks before admission and he had never had an alcohol use disorder. As confirmation, his urine drug screen and blood alcohol levels were negative for these or any other substances. A serum venlafaxine level was not drawn upon admission, which would have been essential supporting evidence of venlafaxine being the culprit for this psychotic episode.

Dennison EA, Raidoo BM, Cruz R, et al. A case of high-dose venlafaxine-related psychosis. *J Clin Psychopharmacol*. 2013; 33(1):134-135.

NEUROLOGIC ADVERSE EFFECTS OF RANOLAZINE

Ranolazine is an antianginal agent that exerts its therapeutic effect via neuronal sodium channels. Ranolazine is approved for the treatment of chronic angina when symptoms persist despite the use of first-line therapies such as nitrates, beta blockers, and calcium channel blockers.

An 81-year-old Caucasian woman was admitted to the hospital with complaints of substernal chest pain. Her medication regimen prior to admission was aspirin 81 mg daily, metoprolol tartrate 12.5 mg twice daily, clopidogrel 75 mg daily, rosuvastatin 5 mg daily, nitroglycerine SL 0.4 mg as needed, citalopram 40 mg daily, omeprazole 40 mg twice daily, and allopurinol 300 mg daily. At baseline, the patient had some early signs of dementia, including word-finding difficulties and short episodes of agitation associated with confusion.

The patient's troponin T level was 1.3 ng/mL (reference level, 0.0 ng/mL) and a CK-MB level of 36 ng/mL (reference range, 0.0-6.6 ng/mL) but no evidence of EKG changes. Her liver function tests were within normal limits, and her serum creatinine was elevated at 1.6 mg/dL (reference range, 0.5-1.2 mg/dL) with an estimated creatinine clearance of 20 mL/min. The patient received a cardiac catheterization but was deemed not a candidate for surgical intervention, so optimization of her antianginal medications was initiated. Ranolazine was initiated at 500 mg twice daily because up-titration of her metoprolol was not feasible due to heart rate and blood pressure restrictions.

On hospital day 3, her ranolazine dosage was increased to 1,000 mg twice daily, and isosorbide

dinitrate 10 mg 3 times daily was initiated because the patient was continuing to experience intermittent chest pain. Four days after ranolazine initiation, the patient exhibited mild confusion and word-finding difficulties. On this day, her serum creatinine had risen to 1.9 mg/dL; dehydration and exposure to contrast media during her catheterization were thought to have contributed to her worsening renal function. Day 5 brought increased central nervous system symptoms including dysarthria, dysmetria, increased word-finding difficulties, and difficulty with ambulation due to intense tremors and hallucinations. On day 5, ranolazine was discontinued and within 2 days her neurologic signs and symptoms markedly improved. Four weeks after discharge, the patient did not display dysarthria, dysmetria, tremors, or hallucinations.

The authors theorize that because ranolazine has a piperazine ring in its chemical structure, it may be responsible for the neurologic adverse effects exhibited by the patient. It should be noted that a piperazine ring is also a part of many psychotropic drugs, including antidepressants, antipsychotics, and illicit hallucinogens. Ranolazine is also structurally similar to lidocaine and was thought to have therapeutic potential for the treatment of pain syndromes during the drug development process. Animal studies utilizing high doses of ranolazine observed neurologic adverse effects of bradykinesia, motor sluggishness, muscle fasciculations, twitching, and convulsions. The pharmacokinetics of ranolazine are considerably affected by age and hepatic and renal impairment.

The authors made the following recommendation, "Patients with underlying neurologic disease, even when mild, should be monitored carefully when initiating or increasing the dose of ranolazine. Elderly patients with age-related decreases in renal and hepatic function are at increased risk of elevated ranolazine serum concentrations and, thus, adverse effects. We recommend a maximum ranolazine dosage of 500 mg twice daily for patients who are older than 80 years or who have a creatinine clearance of less than 30 mL/min."

Southard RA, Blum RM, Bui AH, et al. Neurologic effects of ranolazine in an elderly patient with renal impairment. *Pharmacotherapy*. 2013;33(1):e9-e13. ■