

Acute benzodiazepine toxicity exacerbated by concomitant oral olanzapine

Marc S Hoffmann, MD,^{a†} Michael J Overman, MD,^b and Joseph L Nates, MD, MBA^c

^aUniversity of Kansas Cancer Center, Overland Park, Kansas; and ^bDepartment of Cancer Medicine and ^cDepartment of Critical Care, MD Anderson Cancer Center, Houston, Texas.

Improvements in antiemetic therapy constitute a major advance in oncology. A recent poll of the oncology community by the American Society of Clinical Oncology ranked it as one of the top 5 advances in cancer in the last 50 years.¹ Emetogenicity of chemotherapy is defined by risk of emesis in the patient given no antiemetics; high-risk regimens cause nausea and vomiting in >90% of patients, moderate risk in 30%-90%, and low risk in <30%. This risk profile serves as the basis for empiric antiemetic prophylaxis and offers alternatives to refractory patients. Modern antiemetic prophylaxis is extremely effective for high-risk chemotherapy, reducing the risk for breakthrough nausea and vomiting to 0%-13% in the acute setting (<24 hours from receipt of chemotherapy) and to 25%-30% in the delayed setting (24-72 hours from receipt of chemotherapy).²

Current guidelines from the National Comprehensive Cancer Network (NCCN) offer 3 preferred regimens of equal efficacy for antiemetic prophylaxis of highly emetogenic chemotherapy.³ For all 3 of those regimens, a footnote suggests that the benzodiazepine lorazepam 0.5-2 mg intravenously (IV) or sublingual can be administered every 6 hours as an adjunct. Two of the preferred regimens combine a neurokinin-1 (NK-1) antagonist (aprepitant, fosaprepitant dimeglumine, or netupitant) with a serotonin (5-HT₃) antagonist (ondansetron, palonosetron, granisetron, or dolesetran). In the first regimen, the NK-1 and 5-HT₃ antagonists are administered as separate agents, and the second regimen is a fixed-dose oral combination. In both regimens, dexamethasone is taken on days 1, 2, 3, and 4. In 2011, a combination based on the antipsychotic olanzapine demonstrated comparable efficacy to an aprepitant-based regimen in a phase 3 randomized trial.² This regimen constitutes the third preferred regimen and contains oral olanzapine 10 mg daily

on days 1, 2, 3, and 4; the long-acting 5-HT₃ antagonist palonosetron and dexamethasone are given on day 1 only. Although the mechanism of action is not clearly understood, olanzapine is thought to block both 5-HT₃ and dopamine receptors, and may distinguish between pure NK-1 and 5-HT₃ antagonists.⁴ By including a novel drug class, limiting steroid exposure, and reducing pill burden, olanzapine-based regimens are an attractive option as a front-line therapy and in patients who are refractory to NK-1 antagonist-based regimens.

There have been reports of severe drug reactions leading to hypotension, respiratory depression, and hypoaffective delirium in patients who receive the combination of intramuscular (IM) olanzapine and lorazepam.^{5,6} The mechanism of this interaction remains unknown. These observations led the manufacturer to issue a warning against combining benzodiazepines with IM olanzapine on the package insert.⁴ Subsequently, a similar reaction was reported with oral olanzapine and oral lorazepam in the psychiatric population.⁷ However, this reaction has not been reported when the drugs are combined as antiemetics for chemotherapy-induced nausea and vomiting (CINV).

Herein, we describe a severe reaction of hypotension, respiratory depression, and hypoaffective delirium observed in a cancer patient taking oral olanzapine and lorazepam for CINV.

Case presentation and summary

The patient was a 61-year-old woman who was undergoing treatment at the MD Anderson Cancer Center in Houston, Texas, for pancreatic cancer that had metastasized to the lung, liver, and lymph nodes. She was being treated with dose-attenuated oxaliplatin with fluorouracil (5-FU) and folinic acid (FOLFOX) chemotherapy (oxaliplatin 60 mg/m² IV over 2 hours, 5-FU 2000 mg/m² IV over 46

Accepted for publication July 21, 2015. †Dr Hoffmann is now a hematology-oncology fellow at MD Anderson Cancer Center, Houston Texas. Correspondence: Marc S Hoffmann, MD; mhoffmann@kumc.edu. Disclosures: The authors have no conflicts of interest or financial disclosures. JCSO 2016;14:178-179. ©2016 Frontline Medical Communications. doi: 10.12788/jcso.0187.

hours) and had persistent nausea that had not been responsive to multiple prior interventions. She had been taking lorazepam 1 mg orally 2-3 times daily for several months previous to manage her nausea and anxiety. Starting the day of chemotherapy, the patient began a prescription of oral olanzapine 10 mg daily for 10 days for the prevention of chemotherapy-induced delayed nausea and vomiting. On the day of chemotherapy, she took lorazepam 1 mg orally at 1:00 pm and olanzapine 10 mg orally at 3:15 pm just before starting her chemotherapy. She was given an additional dose of lorazepam 1 mg intravenously as a premedication for her chemotherapy at about 3:45pm. She completed the 2-hour infusion of oxaliplatin and had the 5-FU pump connected to her port.

At the time of pump connect, she was delirious and unresponsive. Vital signs revealed a respiratory rate of 6-8 breaths per minute (normal, 12-20), with systolic blood pressure in the 70-80 (normal, >90 mmHg). She was transferred to the emergency department from the infusion suite. She received 0.5 mg IV flumazenil at 8:00 pm for presumptive benzodiazepine toxicity with dramatic resolution of her symptoms. She had recurrent hypotension, respiratory depression, and delirium about an hour later and was admitted to the intensive care unit (ICU). Complete blood count, electrolytes, liver function tests, and coagulation parameters were normal except for glucose of 196, hemoglobin of 10.8 mg/dL (normal, 12-14 mg/dL), and D-dimer of 1.6 mcg/mL (normal, <0.4 mcg/mL). Cardiac enzymes, morning cortisol, thyroid stimulating hormone, and blood cultures were negative, and a urine culture showed mixed flora consistent with contamination with no pyuria on urinalysis, indicating a lack of other clear explanations for her acute hypotension. She denied any previous alcohol or illicit drug ingestion. The patient needed a total of another 4 doses of flumazenil 0.5 mg, the last of which was delivered at 2:15 am the following morn-

ing. She had a complete recovery and did not develop any additional reactions. She was diagnosed with acute benzodiazepine toxicity exacerbated by olanzapine and discharged in stable condition.

Discussion

This case of acute benzodiazepine toxicity exacerbated by olanzapine when given in the oral formulation confirms the potential for severe toxicity with oral formulations in both the psychiatric⁶ and supportive care settings. The mechanism for this interaction remains unknown. The fact that toxicity seems more common when the agents are administered intravenously or intramuscularly suggests that toxicity is likely a peak drug effect. The response to flumazenil suggests a primary component of exacerbated benzodiazepine toxicity; however, features of olanzapine toxicity (somnolence, hypotension) overlap with benzodiazepine toxicity⁸ and confound attribution. Metabolic interactions do not seem to be significant: olanzapine is metabolized by CYP1A2 and CYP2A6, although CYP2A6 is a minor pathway;⁴ lorazepam undergoes extensive hepatic metabolism independent of the cytochrome system then excreted in the urine.⁹ The treatment team should know that: olanzapine and benzodiazepines can have a potentially fatal interaction through an unknown mechanism of action when they are co-administered; the toxicity can occur regardless of route of administration; and flumazenil is an effective drug for managing this toxicity.

Given the severity of this potentially fatal reaction, it is important for pharmacists and oncologists to be aware of this toxicity when prescribing these medications. In addition, current National Comprehensive Cancer Network guidelines and the olanzapine package insert may need to include a reminder to users of this serious adverse reaction for not only the intramuscular but also the oral combination of olanzapine and benzodiazepines.

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