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CASE REPORT

REMISSION OF CHEMOTHERAPY-INDUCED EMESIS WITH CONCURRENT OLANZAPINE TREATMENT: A CASE REPORT

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INTRODUCTION

Chemotherapy-related nausea and vomiting affect at least half of the patients receiving chemotherapy (Morrow and Dobkin, 1988; Morrow *et al*., 1998). They can be severe and lead to conditioned responses that linger even years later. Although newer antiemetic medications, such as ondansetron and granisetron, have been developed over the last decade, chemotherapy-induced nausea and vomiting still remain a difficult problem. Sometimes nausea and vomiting may persist in patients after all current antiemetic treatments have been exhausted (Gawande, 1999).

Psychiatric medications have played a prominent role in the battle against nausea. In recent years, benzodiazopines, such as lorazopam and alprazolam, have been used to ease chemotherapy-induced nausea, particularly anticipatory or conditioned nausea. There has also been some suggestion that nefazadone, an atypical antidepressant, may have antiemetic effect (Khouzam *et al*., 1998). However, many medications used to treat nausea fall into the antipsychotic class. Typical antipsychotics, particularly phenothiazines (prochlorperazine) and butyrophenones (droperidol and haloperidol), and other medications with antipsychotic-like structures, such as metoclopramide, are widely used in cancer treatment as antiemetics. These medications work by blocking brain dopamine receptors in the chemotrigger zone (CTZ) of the medulla (Veyrat-Follet *et al*., 1997). However, the antiemetic effect is thought to be mainly from antagonism of the D2 receptor, which can also commonly cause unwanted extrapyramidal side effects, such as akasthisia, dystonia, and even tardive dyskinesia (Stefanini and Clement-Cormier, 1981; Breitbart, 1986; Leslie *et al*., 1990).

Newer atypical antipsychotic medications, such as clozapine, respiradone and olanzapine, are less likely to produce extrapyramidal side effects because of their weaker affinity for the D2 receptor, but have not been used as antiemetics. Clozapine requires close monitoring because of its risk for agranulocytosis, an unacceptable additional risk in cancer patients already receiving marrow-suppressing chemotherapy. Risperidone and olanzapine have much safer side effect profiles and do not require close monitoring. Although risperidone has been shown to have antiemetic effect in animals, there have not been any reports of risperidone or other atypical antipsychotics acting as antiemetics in humans (*Physicians' Desk Reference*, *1999*).

We report a case of a woman with leukemia and chemotherapy-induced emesis, seen recently at Memorial Sloan-Kettering Cancer Center, who was treated with olanzapine for psychiatric reasons that may suggest some antiemetic effect from this drug.

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CASE

A 41-year-old woman with recurrent acute lymphocytic leukemia (ALL), and a history of depression and anxiety, was admitted for chemotherapy with cytosine arabinoside, idarubicin and intrathecal methotrexate.

Prior to her cancer diagnosis, she was being treated for her depression and reported to be doing well on fluoxetine and lorazopam. However after her diagnosis she said that 'everything came crashing down'. Even before her admission, she began paging the on call psychiatrist almost daily in the middle of the night. However, she would not follow up with scheduling an appointment.

She gave vague descriptions of her affective state and was not able to elaborate beyond the terms, 'depressed' and 'anxious'. She described borderline dynamics throughout her life (fears of abandonment, chronic feelings of emptiness, and intense, conflictual relationships) but had no history of psychiatric hospitalizations or physically self-destructive behaviors.

Two days into her chemotherapy she began having severe nausea, accompanied by vomiting. Prior to her chemotherapy infusion, she was premedicated with ondansetron 8 mg and dexamethasone 20 mg. For 4 days, starting with the infusion of her chemotherapy, she received ondansetron 8 mg once daily (qd), dexamethasone 20 mg qd, and lorazepam 2 mg IV every 8 h. Her vomiting continued and she was given one dose of prochlorperazine 10 mg that resulted in unbearable extrapyramidal side effects. She developed 'anxiety' and restlessness, stating, 'I feel panicky, like I am going to jump out the window'. The following day, she received a dose of metoclopramide 10 mg and developed similar symptoms. Upon discontinuation of these medications, her akathesia resolved.

However, 1 week after the chemotherapy infusion, her nausea and vomiting persisted and she became more emotionally labile. She received lorazepam 2 mg intravenously (IV) every 6 h without relief. Ondansetron 8 mg IV qd was reinstituted and one dose of cisapride 10 mg was used because of its effect on gastrointestinal motility and similarity in structure to other antiemetics. She still complained of nausea and vomiting.

She became increasingly agitated, emotionally labile, and more difficult for the staff to manage. She would constantly call her nurses, crying and enraged. Psychiatry was called at that time.

PAST PSYCHIATRIC HISTORY

The patient had no history of psychiatric hospitalizations or suicide attempts. She had seen a psychiatrist 'years ago' who started her on fluoxetine and lorazopam. Her primary care doctor and oncologist continued her on these medications.

MEDICAL HISTORY

The woman was diagnosed with acute lymphocytic leukemia 1 year before this admission. She had no other medical or surgical problems. The week after receiving her chemotherapy, she developed fever and neutropenia and was started on antibiotics.

At the time of her psychiatry consult, her medications included fluoxetine 40 mg qd, lorazepam 2 mg IV q6 h, vancomycin 1 g IV q12 h, granulocyte colony stimulating factor (GCSF) 480 mg SQ q12 h, gentamicin 100 mg IV q6h, amphotericin B 60 mg IV qd, ticarcillin-clavulanic acid 3.1 g IV q4 h, ranitidine 150 mg twice daily (bid), docusate 100 mg three times daily (tic), and ondansetron 8 mg IV qd.

She had no known drug allergies.

SOCIAL HISTORY

The patient was living with her husband, who has bipolar disorder, and four children. She completed some college and worked at home as a free lance writer. She denied using tobacco, alcohol, and drugs.

MENTAL STATUS EXAM

The patient was a large woman wearing a turban, lying in a completely darkened room. Her room was cluttered with multiple stuffed animals and large portraits of her children. Her speech was dramatic but fluent. Her MMSE score was 30/30. She described her mood as 'depressed' and her affect was shallow and labile, frequently alternating

from crying to laughing. Her thought was linear and she denied psychotic symptoms. She endorsed some neurovegetative symptoms of depression, mainly insomnia, helplessness, decreased energy, poor concentration, and decreased appetite. She denied suicidal and homicidal ideation.

HOSPITAL COURSE

Although the patient did seem to be depressed on evaluation, her extreme mood lability and demands on the staff appeared consistent with borderline personality disorder. These patterns seemed to be present even before she was started on dexamethasone with her chemotherapy. We initially increased her fluoxetine to 60 mg qd for her depressive symptoms. As her lability and intermittent agitation continued unchanged over the next 3 days, we started olanzapine 5 mg before bedtime (qhs). The following day, she reported 'feeling better' and also noted that her nausea had resolved. Although her depressive symptoms continued, she remained free of nausea and vomiting on ondansetron 8 mg qd, lorazepam 2 mg four times a day (qid) and olanzapine 5 mg qhs.

DISCUSSION

Olanzapine is an atypical antipsychotic that affects many different neurochemical systems, including dopamine, serotonin, the catecholamines, acetylcholine and histamine. It produces its antipsychotic effect by blocking dopamine at the D2, D1 and D4 receptors in the brain. Its weak affinity for the D2 receptor leads to less extrapyramidal symptoms. Olanzapine blocks serotonin at the 5-HT2a, 5-HT2c, and 5HT3 receptors, catecholamines at alpha-1 adrenergic receptors, acetylcholine at muscarinic receptors and histamine at H1 histaminic receptors (Bymaster *et al*., 1996). Its common side effects include sedation and weight gain (Hale, 1997). Recently, it has been associated with the onset of diabetes and even ketoacidosis (Goldstein *et al*., 1999).

Olanzapine may have antiemetic activity from two separate mechanisms. First, similar to typical antipsychotics, it blocks the D2 dopamine receptors. However, its D2 antagonism is weaker than typical neuroleptics, less than 40% of the affinity of haloperidol (Richelson, 1996)

As a second possible mechanism, olanzapine blocks serotonin receptors that have been shown to provide antiemetic effect. Olanzapine blocks the 5-HT3 serotonin receptor, the main mechanism of action of one of the most powerful antiemetics, ondansetron. These serotonin receptors are located in the gut (Andrews and Davidson, 1990). Olanzapine may not only have some theoretical efficacy advantage over typical antipsychotics for nausea by blocking both dopamine and 5-HT3 receptors, but it is also less likely to cause extrapyramidal symptoms.

In this case, olanzapine was used in combination with standard antiemetics. There have been no reports of olanzapine used as a single agent for nausea and vomiting. However, only a portion of patients is now controlled on just a single agent. Combination antiemetic therapy has become more popular and has been shown to be more effective (Stewart, 1990). Olanzapine may have a role in this combination therapy.

Although olanzapine may be an expensive new antipsychotic, it is still less than half the price of the newer antiemetic medications. Olanzapine's once a day dosing (qhs) also may decrease the complexity and cost of treatment.

In conclusion, more research is needed to determine if olanzapine can be used as an effective, costefficient antiemetic medication.

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