Case Report

Olanzapine induced delirium—a "probable" adverse drug reaction

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Abstract: Olanzapine is an atypical antipsychotic indicated for the treatment of schizophrenia and known to be effective in the management of delirium. In addition to its use for these indications olanzapine has also been used in the management of chemotherapy induced nausea and vomiting and otherwise difficult to control nausea and vomiting in palliative care settings. Although considered to be well tolerated with a lower incidence of extrapyramidal effects than first generation antipsychotics there are a small number of reports of olanzapine inducing delirium. Reported here are two cases of "probable" acute cognitive impairment following treatment of nausea with olanzapine. The cognitive impairment associated with olanzapine is probably mediated through its activity at cholinergic receptors a known risk factor for delirium particularly in the elderly.

Keywords: Olanzapine; delirium; adverse drug reaction

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Introduction

Olanzapine is an atypical antipsychotic indicated for the treatment of schizophrenia and known to be effective in the management of delirium. In addition to its use for these indications olanzapine has also been used in the management of chemotherapy induced nausea and vomiting (1,2), and otherwise difficult to control nausea and vomiting in palliative care settings (3,4). Although considered to be well tolerated with a lower incidence of extrapyramidal effects than first generation antipsychotics (5), there are a small number of reports of olanzapine inducing delirium (6-10). Reported here are two cases of "probable" acute cognitive impairment following treatment of nausea with olanzapine.

Case presentation

Case 1

AB was a 75-year-old male with a recto-sigmoid adenocarcinoma and liver metastases. Co-morbidities included insulin dependent diabetes mellitus, hypertension, second degree heart block with an implanted cardiac pacemaker, hypercholesterolaemia and macular degeneration.

AB had been experiencing pain and nausea both of which had been poorly controlled. Pain was being managed with extended release morphine 10 mg twice daily with immediate release oxycodone 5 mg for breakthrough pain. Nausea was persistent and had failed to respond adequately to haloperidol 1.5 mg twice daily. Other medications included fluconazole, loperamide, allopurinol and Novomix 30 insulin.

Following the consultation AB agreed to increase the dose of extended release morphine to 20 mg twice daily and to trial olanzapine 5 mg at night for the nausea. Both the haloperidol and fluconazole were discontinued.

AB slept well that night and did not wake until the middle of the following day. During that afternoon and evening AB's family noted that he had become confused, wandering around the house and unable to conduct appropriate conversation. Over the next 24 hours AB's cognition gradually improved and he returned to his previous cognitive state which was considered to be normal.

Although no formal assessment was made during the period of altered cognition the family members' description of the episode is consistent with an acute delirium—acute onset with fluctuating course, inattention and disorganised thinking.

Case 2

CD was a 69-year-old man with adenocarcinoma of the prostate and bony metastases. Co-morbidities included hypertension and dyslipidaemia. For 2 months he had been troubled with persistent nausea which had failed to respond to metoclopramide 10 mg 3 times a day, haloperidol 1 mg twice daily and cyclizine 25 mg up to 3 times a day either alone or in combination. Onset of the nausea appeared to be temporally related to commencing treatment with enzalutamide. Concurrent medication included sustained release oxycodone, aspirin, esomeprazole, paracetamol (acetaminophen), denosumab, vitamin D, calcium supplement and oral potassium supplement.

Following discussion, CD agreed to a trial of olanzapine 5 mg at night which was increased to 10 mg after 2 doses due to lack of efficacy. Other antiemetics were discontinued. Between 12 and 24 hours after increasing the dose of olanzapine to 10 mg, CD became increasingly agitated. He was unable to carry on a coherent conversation and developed what appeared to the family observers to be frightening hallucinations. No further doses of olanzapine were administered and the symptoms resolved over the subsequent 24 hours. No other changes to drug treatment were made during the period of interest. CD had no recall of the events in question which were described by attending family members. Based on their description, this episode satisfies the criteria for an episode of agitated delirium—acute onset with fluctuating course, inattention and disorganised thinking. Resolution was spontaneous.

Discussion

The Naranjo scoring system for estimating the probability of an adverse drug reaction having occurred provides a consistent, reproducible structure for making such a determination (11). The scoring system places particular emphasis on the temporal relationship between drug administration and development of signs and symptoms and exclusion of alternative explanations for the observed response. In both the cases described, the estimated probability of an adverse drug reaction having occurred was "probable"; scoring between 5 and 8. The remaining scoring categories are ≥9 "definite", 1 to 4 "possible" ≤0 "doubtful".

AB's symptoms developed after administration of a single dose of olanzapine 5 mg. The time of onset is unknown as AB experienced a long period of sleep following the dose of olanzapine. The symptoms lasted for several hours and subsequently took a number of hours to resolve spontaneously. In the case of CD, symptoms did not appear until the dose of olanzapine was increased to 10 mg but followed a similar time course to eventual spontaneous resolution.

No convincing alternative causes present themselves in either case. No other new medications were prescribed and withdrawal of olanzapine without additional therapy was associated with resolution of the symptoms. With AB, the dose of extended release morphine should have been increased to 20 mg (10 mg tablets ×2). However, the family found one 10 mg tablet on the floor the following morning and were confident that AB had only ingested a single 10 mg tablet. Subsequent dosing with extended release morphine 20 mg twice daily was uneventful. Routine blood glucose monitoring showed no evidence of hypoglycaemia. The only identified change in CD's case was the increase in the dose of olanzapine. Although no pathology testing was carried out in either case, what appears to have been spontaneous resolution of symptoms does not support the presence of other unidentified metabolic or pathological processes as a cause for the cognitive changes observed. Confirmatory re-challenge with the possible offending agent was not undertaken. Olanzapine has a time to maximum concentration of 5 to 8 hours and an elimination half-life 21 to 54 hours, tending to be longer in the elderly (>65 years) (12,13). This pharmacokinetic profile is consistent with the time course of these episodes and their resolution.

As noted above, there are a small number of reports of olanzapine inducing delirium most probably through its activity at the muscarinic cholinergic receptor. Further support for this can be found in reports of successful treatment of cognitive symptoms of olanzapine poisoning with the cholinesterase inhibitor physostigmine (14). Drugs with anticholinergic activity and which cross the blood brain barrier are known precipitants of delirium particularly in the elderly (15).

Interestingly, CD had been able to tolerate the anticholinergic antihistamine cyclizine 25 mg without any apparent adverse effects. However, when the dose was later increased to 50 mg CD developed acute cognitive

impairment as reported by his family.

AB and CD "probably" represent cases of olanzapine induced delirium. With increasing interest in alternative treatments for nausea and vomiting in palliative care it is likely that we will see an increased use of olanzapine in this population. The end of life is a period associated with a high incidence of cognitive impairment frequently managed with antipsychotic medication. Palliative care practitioners should be aware of the paradoxical property of olanzapine to induce delirium, albeit at low frequency, and the resulting need to reduce or discontinue the drug rather than increase it. Haloperidol is a suitable alternative if antipsychotic medication is required and there is doubt about the aetiology of a delirium. Its efficacy at the end of life in the management of delirium is established and it has the advantage of being available in an injectable form (16).

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None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

Informed Consent: Informed consent has not been obtained. One patient is now deceased and the family are not contactable. The second patient is still alive but would not be discoverable from the information disclosed in the manuscript.

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